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Carotid Stenting With Antithrombotic Agents and Intracranial Thrombectomy Leads to the Highest Recanalization Rate in Patients With Acute Stroke With Tandem Lesions

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ABSTRACT

OBJECTIVES The aim of this study was to identify the optimal endovascular approach in patients with acute stroke with tandem lesions.

BACKGROUND At present, there is no consensus about the ideal technical strategy for the endovascular treatment of patients with acute ischemic stroke with tandem lesions of the extracranial internal carotid artery (ICA) and intracranial cerebral arteries.

METHODS This was an international, multicenter registry with a total of 482 patients with acute ischemic stroke and tandem lesions. Patients were treated by intracranial thrombectomy as well as 1 of the following 4 strategies: 1) acute carotid artery stenting of the extracranial ICA with antithrombotic agents; 2) acute carotid artery stenting of the extracranial ICA without antithrombotic agents; 3) balloon angioplasty of the extracranial ICA; and 4) intracranial thrombectomy alone. The main outcome endpoints of the study were the degree of recanalization and the 90-day clinical outcome. The safety endpoints were symptomatic intracerebral hemorrhage and all causes of mortality at 90 days.

RESULTS Using univariate analysis, the rates of successful reperfusion (modified Thrombolysis in Cerebral Infarction grades 2B and 3) and favorable clinical outcome after 90 days were significantly higher after acute carotid stenting with antithrombotic therapy and thrombectomy compared with the group with thrombectomy alone. After adjusting for confounding variables, acute stenting with antithrombotic therapy was independently associated with successful recanalization (odds ratio: 2.4; 95% confidence interval: 1.25 to 4.59; $p = 0.008$). The rates of symptomatic intracerebral hemorrhage and 90-day mortality were comparable among all 4 treatment groups.

CONCLUSIONS Acute stenting of the extracranial ICA with antithrombotic therapy in combination with intracranial thrombectomy is associated with higher recanalization rates in treatment of patients with acute stroke with tandem lesions. (J Am Coll Cardiol Intv 2018;11:1290–9) © 2018 by the American College of Cardiology Foundation.

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Tandem lesions in patients with acute ischemic stroke (AIS) are a combination of high-grade stenosis or occlusion of the extracranial segment of the internal carotid artery (ICA) with concurrent occlusion of an intracranial vessel (1,2). The treatment of tandem lesions represents a considerable challenge because intravenous (IV) thrombolysis achieves recanalization in only 4% to 32% of cases, depending on the site of occlusion. Treating tandem lesions with standard IV thrombolysis alone leads to good clinical outcomes in only 17% of cases, with a death rate as high as 55%. Because these lesions, in the setting of AIS, are therapeutically challenging (3), they are often excluded from randomized clinical trials (4–7). Moreover, tandem lesions are not common compared with isolated intracranial occlusion; patients with tandem lesions account for only up to 20% of participants in trials in which they are included.

SEE PAGE 1300

The HERMES meta-analysis of recent randomized AIS trials included only 122 patients with tandem lesions and demonstrated that endovascular treatment (EVT) is more beneficial than the standard treatment using IV thrombolysis with tissue plasminogen activator (tPA) (8,9). However, there is currently no consensus about the ideal technical interventional strategy for tandem lesions. Therapeutic approaches vary, especially regarding treatment of the extracranial lesion. Some interventionists perform acute extracranial ICA stenting, whereas others prefer to perform only balloon dilatation. Alternatively, the extracranial ICA lesion may not be treated at all (10). There is also no agreement regarding the antithrombotic regimen, as the potential benefit of reducing ischemic complications with antithrombotic therapy must be balanced with the risk for reperfusion hemorrhage (10).

The principal aim of this study was to identify the best therapeutic treatment strategy for patients with AIS with tandem lesions by comparing the outcomes of different endovascular approaches in a large multicenter data pool consisting of 482 individual cases.

ABBREVIATIONS AND ACRONYMS

AIS = acute ischemic stroke
CI = confidence interval
EVT = endovascular treatment
ICA = internal carotid artery
IV = intravenous
mRS = modified Rankin Scale
mTICI = modified Thrombolysis in Cerebral Infarction
NIHSS = National Institutes of Health Stroke Scale
OR = odds ratio
sICH = symptomatic intracerebral hemorrhage
tPA = tissue plasminogen activator

METHODS

PATIENTS AND SELECTION CRITERIA. Patients were pooled from 18 endovascular databases and included consecutive patients with AIS with tandem lesions of the anterior circulation treated with EVT. Among the participating sites were 6 centers in France, 5 centers in Germany, 3 centers in the United States, and 1 center each in Spain, Austria, Italy, and Denmark. Detailed materials have previously been reported (11). The study was approved by local Institutional Review Boards.

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Dr. Papanagiotou is a local principal investigator for the SWIFT PRIME study; and has served as a consultant for Penumbra and Johnson & Johnson. Dr. Holtmannspötter has received honoraria for consultancy and proctoring from Medtronic, Stryker, and Microvention. Dr. Nogueira has received honoraria from Stryker Neurovascular for the TREVO 2 trial and DAWN trial, from Medtronic for the SWIFT and SWIFT PRIME trial steering committees, and STAR trial core laboratory, from Penumbra for 3D Separator Trial Executive Committee, and from Neuravi for the ARISE-2 steering committee. Dr. Siddiqui has received grants from the National Institutes of Health, National Institute of Neurological Disorders and Stroke, and National Institute of Biomedical Imaging and Bioengineering, University at Buffalo; personal fees from Hotspur, Intratech Medical, StimSox, Valor Medical, Blockade Medical, and Lazarus Effect; and nonfinancial support from Codman & Shurtleff, Concentric Medical, ev3/Covidien Vascular Therapies, GuidePoint Global Consulting, Penumbra, Stryker, Pulsar Vascular, MicroVention, Lazarus Effect, and Blockade Medical, outside the submitted work. Dr. Spiotta owns stock in Penumbra; and has received honoraria for consultancy and proctoring for Penumbra and Stryker. Dr. Turjman has received honoraria for consultancy and proctoring from Medtronic, Stryker Codman, and Balt. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Patients were included in this study if they had tandem lesions, defined as extracranial ICA lesions (complete occlusion or severe stenosis of ≥90% NASCET [North American Symptomatic Carotid Endarterectomy Trial]) and proximal intracranial occlusions (distal ICA and/or M1 and/or M2 segment of the middle cerebral artery). The treatment and therapeutic approach of the extracranial ICA lesion, as well as the type of antithrombotic therapy, was left to the discretion of the interventionalists. All intracranial occlusions were treated using modern mechanical devices such as stent retriever and/or contact aspiration. Patients with isolated extracranial ICA lesions were excluded from this analysis.

INTERVENTIONAL TREATMENT AND ANTITHROMBOTIC AGENTS. Patients were divided into 4 groups depending on the therapeutic strategy used: group 1, acute stenting of the extracranial ICA lesion with antithrombotic agents and intracranial thrombectomy; group 2, acute stenting of the extracranial ICA lesion without antithrombotic agents and intracranial thrombectomy; group 3, balloon angioplasty of the extracranial ICA lesion and intracranial thrombectomy; and group 4, intracranial thrombectomy without treatment of the extracranial ICA lesion.

Because the different participating centers used different medication regimes with regard to type, dose, and time of administration of the drugs, our analysis focused exclusively on the number of agents that were used. In the acute phase, the different types of antithrombotic regimen used included IV aspirin, IV glycoprotein IIb/IIIa receptor antagonist, clopidogrel, and heparin. Seventy-four percent of included patients received antithrombotic drugs during the procedure, and 61.5% were treated with IV thrombolysis before interventional treatment.

OUTCOME PARAMETERS. The coprimary endpoints of the study were the degree of recanalization and the 90-day clinical outcome. Clinical outcome was assessed by applying the modified Rankin Scale (mRS) at 90 days. The mRS scores were obtained either during face-to-face follow-up or through telephone interviews conducted according to study protocol. Favorable outcome was defined as a 90-day mRS score of ≤2. Successful recanalization of the occluded target vessel was defined as achieving a grade of 2B or 3 in the modified Thrombolysis in Cerebral Infarction (mTICI) classification at the end of the procedure.

The safety endpoints were symptomatic intracerebral hemorrhage (sICH) at 24 h and all causes of mortality at 90 days. sICH was defined as any parenchymal hematoma, subarachnoid hemorrhage, or intraventricular hemorrhage associated with worsening of the National Institutes of Health Stroke Scale (NIHSS) score by 4 points or more.

PARAMETER DEFINITIONS. The following variables were collected: age; sex; medical history, including main vascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, and current smoking); initial stroke severity as assessed by NIHSS score on admission; initial imaging modality at admission and Alberta Stroke Program Early CT Score; prior use of IV tPA; intracranial and extracranial occlusion site and type (atherosclerosis or dissection); severity of the extracranial ICA lesion (complete occlusion or stenosis ≥90% NASCET); and types of mechanical devices (stent retrievers and/or aspiration) used. The thrombectomy procedure was monitored for procedure-related complications, and the degree of recanalization was assessed by mTICI grade (12). The time from onset to successful recanalization was monitored with conventional angiography at the end of the procedure.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD and categorical variables as percentages. Bivariate comparisons used the Student's *t*-test for continuous variables and the Wilcoxon test when assumptions were not validated. Chi-square tests (or Fisher exact tests when the expected cell frequency was <5) were used for categorical variables. Four outcomes were investigated: successful recanalization (mTICI grade of 2B or 3), 90-day favorable clinical outcome (90-day mRS score ≤2), 90-day mortality, and sICH. For each outcome, multivariate mixed logistic models were used, including center as a random effect and all univariate predictors at $p < 0.10$ as fixed effects. To avoid bias, multiple imputations using the multivariate imputation by chained equations methodology were applied to account for missing data. The results of each imputed dataset were pooled using Rubin's rules. Statistical testing was done at the 2-tailed α level of 0.05. Data were analyzed using R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PATIENT POPULATION. Among the 482 total patients included in the study, 256 (53%) belonged to treatment group 1 (see "Methods"), 66 (13.7%) to group 2, 52 (10.8%) to group 3, and 108 (22.5%) to group 4.

Table 1 shows the baseline characteristics for each therapeutic approach used. There were no significant

TABLE 1 Baseline Characteristics According to Therapeutic Group

	Thrombectomy and						
	Cervical ICA Stenting With Antithrombotic Agents (Group 1) (n = 256)	Cervical ICA Stenting Without Antithrombotic Agents (Group 2) (n = 66)	Cervical ICA Angioplasty (Group 3) (n = 52)	Thrombectomy Alone (Group 4) (n = 108)	p Value*	p Value†	p Value‡
Age (yrs)	64.1 ± 12.3	63.1 ± 11.8	66.7 ± 8.9	62.1 ± 13	0.168	0.587	0.01
Men	160 (62)	49 (74)	36 (69)	68 (63)	1.00	0.17	0.547
Medical history							
Hypertension	155 (61)	35 (53)	34 (65)	53 (49)	0.057	0.726	0.077
Hypercholesterolemia	105 (41)	17 (26)	24 (46)	36 (33)	0.209	0.377	0.163
Diabetes	32 (12)	21 (32)	14 (27)	16 (15)	0.67	0.014	0.105
Current smoking	92 (36)	14 (21)	20 (38)	29 (27)	0.119	0.512	0.19
NIHSS score§	15 ± 6.2	17.4 ± 6.1	17 ± 4.1	16.5 ± 5.4	0.024	0.337	0.523
ASPECTS‖	8.2 ± 1.6	7.3 ± 1.9	7.5 ± 1.7	7.2 ± 2.1	<0.001	0.715	0.318
Prior IV thrombolysis	156 (61)	43 (65)	32 (62)	65 (60)	0.987	0.621	1.00
Time from symptoms to thrombolysis (min)¶	126.8 ± 49	149.7 ± 49	132.7 ± 61.8	151.5 ± 62.7	<0.001	0.835	0.075
Cervical ICA lesion type					0.091	0.325	0.106
High-grade stenosis ≥90%	126 (49)	20 (30)	28 (54)	42 (39)			
Complete occlusion	130 (51)	46 (70)	24 (46)	66 (61)			
Cervical ICA lesion etiology					0.01	0.065	<0.001
Atherosclerosis	173 (68)	42 (64)	46 (88)	68 (63)			
Dissection	52 (20)	15 (23)	3 (6)	35 (32)			
Cardioembolic	31 (12)	9 (14)	3 (6)	5 (5)			
Intracranial occlusion location					0.349	0.469	1.00
ICA	93 (36)	16 (24)	16 (31)	33 (31)			
MCA	163 (64)	50 (76)	36 (69)	75 (69)			
General anesthesia	139 (54)	47 (71)	16 (31)	45 (42)	0.037	<0.001	0.248
Timing (min)							
Time from symptoms to puncture#	279.8 ± 213.1	292.6 ± 144.6	273.3 ± 139.8	280.8 ± 157.6	0.962	0.614	0.763
Time from puncture to mTICI grade 2B or 3**	76.2 ± 41.7	87.3 ± 52.9	81.6 ± 53.3	76.1 ± 43.1	0.986	0.149	0.52
Time from symptoms to mTICI grade 2B or 3††	357 ± 224.4	364.7 ± 160.6	342.9 ± 147	353.3 ± 167.5	0.863	0.656	0.692
Acute antithrombotic therapy					<0.001	<0.001	0.926
0	0 (0)	66 (100)	40 (77)	85 (79)			
1	138 (54)	0 (0)	11 (21)	22 (20)			
≥2	118 (46)	0 (0)	1 (2)	1 (1)			

Values are mean ± SD or n (%). *Group 4 versus group 1. †Group 4 versus group 2. ‡Group 4 versus group 3. §One missing value. ‖Sixty-three missing values. ¶Thirty-one missing values. #One hundred thirty-eight missing values. **Two missing values. ††Thirty missing values.

ASPECTS = Alberta Stroke Program Early CT Score; ICA = internal carotid artery; IV = intravenous; MCA = middle cerebral artery; mTICI = modified Thrombolysis in Cerebral Infarction; NIHSS = National Institutes of Health Stroke Scale.

differences among the 4 different treatment groups with regard to patient sex ratios, prior IV thrombolysis, intracranial occlusion location, or time from symptom onset to recanalization. Patients in group 1 had slightly lower NIHSS scores at admission (15.0 vs. 16.5, p = 0.024) and higher Alberta Stroke Program Early CT Score values (8.2 vs. 7.2, p < 0.001) than those in group 4. In addition, group 1 had a shorter time from symptom onset to IV thrombolysis (126.8 min vs. 151.5 min, p < 0.001) as well as a higher rate of general anesthesia used (54% [n = 139] vs. 42% [n = 45]; p = 0.037) than group 4.

ANGIOGRAPHIC OUTCOME. Recanalization was successful more often in group 1 compared with group 4 (83% [n = 213] vs. 60% [n = 65]; p < 0.001) (Table 2), group 2 (73% [n = 66]; p = 0.07), and group 3 (69% [n = 52], p = 0.83), although these latter differences were not statistically significant. Groups 1 and 4 also exhibited significant differences in recanalization rates when only complete recanalization

TABLE 2 Efficacy and Safety Outcomes According to Therapeutic Group

	Thrombectomy and						
	Cervical ICA Stenting With Antithrombotic Agents (Group 1) (n = 256)	Cervical ICA Stenting Without Antithrombotic Agents (Group 2) (n = 66)	Cervical ICA Angioplasty (Group 3) (n = 52)	Thrombectomy Alone (Group 4) (n = 108)	p Value*	p Value†	p Value‡
Recanalization	213 (83)	48 (73)	36 (69)	65 (60)	<0.001	0.129	0.349
90-day favorable outcome	148 (58)	29 (44)	21 (40)	45 (42)	0.007	0.892	1
90-day mortality	24 (9)	12 (18)	6 (12)	18 (17)	0.07	0.96	0.539
Symptomatic hemorrhagic complications	14 (5)	6 (9)	0 (0)	5 (5)	0.944	0.336	0.175

Values are n (%). Recanalization was defined as mTICI grade 2B or 3 at the end of thrombectomy. Favorable outcome was defined as an mRS score of 2 or less. Symptomatic hemorrhagic complications were defined as any parenchymal hematoma, subarachnoid hemorrhage, or intraventricular hemorrhage associated with worsening of NIHSS score of 4 points or more according to ECASS-2 criteria. *Group 4 versus group 1. †Group 4 versus group 2. ‡Group 4 versus group 3.

ECASS = European Cooperative Acute Stroke Study; mRS, modified Rankin Scale; other abbreviations as in Table 1.

(mTICI grade 3) was evaluated (41% [n = 105] vs. 23% [n = 25], p = 0.002) or when the data were adjusted for pre-specified confounding factors (odds ratio [OR]: 1.99; 95% confidence interval [CI]: 1.17 to 3.38; p = 0.011). When comparing patients treated by cervical ICA procedure and intracranial thrombectomy (combining groups 1, 2, and 3) with those treated by intracranial thrombectomy alone (group 4), the successful recanalization rate was significantly higher when a cervical ICA procedure was performed (79.4% [n = 296] vs. 60% [n = 65], p < 0.001) (Table 3). The multivariate model indicated an independent association between successful recanalization (mTICI grade of 2B or 3) and acute carotid stenting of the extracranial ICA lesion with antithrombotic therapy (OR: 2.4; 95% CI: 1.25 to 4.59; p = 0.008) (Table 4).

CLINICAL OUTCOMES. At 90 days, there was a significantly higher rate of favorable clinical outcomes in group 1 compared with group 4 (58% vs. 42%, p = 0.007) (Table 2). Group 1 also performed better than group 2 (44%, p = 0.07) and group 3 (40%, p = 0.84), but these differences were not statistically significant. In multivariate analysis, the adjusted OR of 90-day favorable outcome was 1.45 (95% CI: 0.81 to 2.6; p = 0.21). The rates of 90-day favorable outcome and early neurological improvement were strongly associated with recanalization in both groups. Conversely, the rates of favorable outcome increased as the level of recanalization increased. When comparing patients treated by cervical ICA procedure and intracranial thrombectomy (combining groups 1, 2, and 3) with those treated by intracranial thrombectomy alone (group 4), 90-day favorable outcomes were more frequent in patients treated with cervical ICA procedures (53.4% [n = 197] vs. 41.0% [n = 43], p = 0.025). However, this difference failed to retain statistical significance after pre-specified adjustments (adjusted OR: 1.42; 95% CI: 0.83 to 2.41). There was no evidence of heterogeneity in between-group differences according to prior use of IV thrombolysis (p = 0.68).

TABLE 3 Efficacy and Safety Outcomes When Comparing Treatment of Internal Carotid Artery Lesion Versus No Treatment

	Intracranial Thrombectomy and Cervical ICA Procedure (n = 374)	Intracranial Thrombectomy Alone (n = 108)	Unadjusted Analysis		Adjusted Analysis*	
			OR (95% CI)	p Value	OR (95% CI)	p Value
Successful reperfusion	296/373 (79.4)	65/108 (60.2)	2.54 (1.60–4.03)	<0.001	2.04 (1.18–3.51)	0.011
Complete reperfusion	137/373 (36.7)	25/108 (23.2)	1.93 (1.17–3.16)	0.009	1.60 (0.94–2.73)	0.082
90-day favorable outcome	197/369 (53.4)	43/105 (41.0)	1.65 (1.06–2.56)	0.025	1.42 (0.83–2.41)	0.20
90-day mortality	42/369 (11.4)	18/105 (17.1)	0.62 (0.34–1.13)	0.12	0.56 (0.29–1.09)	0.086
Symptomatic intracerebral hemorrhage	19/373 (4.6)	5/108 (4.6)	1.11 (0.40–3.03)	0.85	1.23 (0.40–3.72)	0.72

Values are n/N (%). ORs were calculated using patients treated by intracranial thrombectomy alone as the reference group. Successful reperfusion was defined as mTICI grade 2B or 3 at the end of thrombectomy. Complete reperfusion was defined as mTICI grade 3 at the end of thrombectomy. Favorable outcome was defined as an mRS score of 0 to 2. Symptomatic intracerebral hemorrhage was defined as any parenchymal hematoma, subarachnoid hemorrhage, or intraventricular hemorrhage associated with worsening of NIHSS score of 4 points or more according to ECASS-2 criteria. *Adjusted for prespecified confounders (age, baseline NIHSS score, and prior IV thrombolysis) and center (including as random effect).

CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 2.

SAFETY ENDPOINTS. There were no differences in sICH rates among the 4 treatment groups, with an overall rate of 5% (n = 25). No association was found between any intracranial hemorrhage and prior IV thrombolysis (OR: 0.7; 95% CI: 0.46 to 1.08; p = 0.11) (Table 4). Also, there was no discernible difference in 90-day mortality among the 4 groups, with an overall rate of 12% (n = 60). Lower age, current smoking, lower NIHSS score and Alberta Stroke Program Early CT Score value, and prior IV thrombolysis were each independent predictors of 90-day mortality (Table 4).

ANTITHROMBOTIC THERAPY. Among patients in group 1, there were no significant differences in efficacy and safety outcomes by type of antithrombotic regimen used (1 vs. at least 2 antithrombotic agents) (Table 5).

DISCUSSION

We conducted a large collaborative analysis of individual patient data pooled from 18 centers in 7 countries to identify the ideal endovascular and antithrombotic strategy for treating patients with AIS with tandem lesions (stenosis ≥90% or occlusion of the extracranial ICA). Our findings demonstrate that a treatment strategy involving acute stenting of the extracranial ICA with the use of antithrombotic agents in combination with intracranial thrombectomy (treatment 1) was associated with higher recanalization rates and better clinical outcomes in the absence of increased sICH rates, compared with 3 other treatment strategies: extracranial carotid stenting without antithrombotic treatment (treatment 2), extracranial carotid angioplasty without stenting (treatment 3), and intracranial thrombectomy alone (treatment 4) (Figure 1).

Among these 4 different treatment strategies, only treatment 1 was independently associated with successful recanalization in the multivariate model (mTICI grade of 2B or 3) and more favorable clinical outcomes (13). Both the recanalization rate and 90-day favorable clinical outcome were significantly higher with treatment 1 (83% and 58%, respectively) compared with treatment 4 (60% and 42%, respectively). They were also higher compared with treatments 2 (73% and 44%, respectively) and 3 (69% and 40%, respectively), although not statistically significant. Recanalization was successful more often when patients were treated with a cervical ICA procedure as well as intracranial thrombectomy (combined groups 1, 2, and 3) compared with when patients were treated by intracranial thrombectomy alone (group 4). This result suggests that the ICA lesions should be treated during the same procedure.

TABLE 4 Multivariate Mixed Logistic Model of Recanalization, 90-Day Favorable Outcome, and 90-Day Mortality

	OR (95% CI)*	p Value
Recanalization		
Thrombectomy		
And cervical ICA stenting without antithrombotic therapy	1.90 (0.81–4.44)	0.138
And cervical ICA stenting with antithrombotic therapy†	2.40 (1.25–4.59)	0.008
And cervical ICA angioplasty	1.05 (0.47–2.34)	0.897
Current smoking	2.02 (1.04–3.94)	0.039
ASPECTS	1.23 (1.06–1.43)	0.006
Prior IV thrombolysis	2.10 (1.29–3.44)	0.003
NIHSS score	0.96 (0.92–1.00)	0.076
90-day favorable outcome		
Age (yrs)	0.95 (0.94–0.97)	<0.001
Thrombectomy		
And cervical ICA stenting without antithrombotic therapy	1.32 (0.62–2.81)	0.473
And cervical ICA stenting with antithrombotic therapy†	1.45 (0.81–2.60)	0.212
And cervical ICA angioplasty	1.14 (0.53–2.48)	0.731
Diabetes	0.85 (0.47–1.53)	0.580
Current smoker	1.17 (0.69–1.97)	0.562
ASPECTS	1.29 (1.11–1.50)	0.001
NIHSS score	0.89 (0.85–0.92)	<0.001
90-day mortality		
Age (yrs)	1.05 (1.02–1.08)	0.001
Thrombectomy		
And cervical ICA stenting without antithrombotic therapy	0.87 (0.34–2.23)	0.778
And cervical ICA stenting with antithrombotic therapy†	0.60 (0.27–1.31)	0.200
And cervical ICA angioplasty	0.85 (0.30–2.44)	0.767
Diabetes	1.32 (0.58–3.01)	0.510
Current smoker	0.41 (0.17–0.97)	0.042
ASPECTS	0.75 (0.62–0.89)	0.001
Prior IV thrombolysis	0.48 (0.25–0.90)	0.022
General anesthesia	1.57 (0.81–3.07)	0.183
NIHSS score	1.14 (1.07–1.22)	<0.001

Recanalization was defined as mTICI grade 2B or 3 at the end of thrombectomy. Favorable outcome was defined as an mRS score of 2 or less. *Values adjusted for prespecified confounders (age, baseline NIHSS score, and prior IV thrombolysis). †At least 1 antiplatelet medication.

Abbreviations as in Tables 1 to 3.

The primary goal of treatment (of either tandem lesions or isolated intracranial occlusions) is successful recanalization of the intracranial vessel (13). Because tandem lesions are characterized by the presence of an extracranial lesion, the typical therapeutic strategy consists of a 2-step approach: 1) pass the stenotic or occluded ICA to access the intracranial lesion; and 2) perform a mechanical recanalization of the occluded intracranial vessel (14,15). All 4 treatment strategies evaluated in the present study differ from this typical approach. We judged each method

TABLE 5 Comparison of Efficacy and Safety Outcomes According to the Type of Antithrombotic Therapy in the Thrombectomy and Cervical Internal Carotid Artery Stenting Group

	Thrombectomy and Cervical ICA Stenting With		
	1 Antithrombotic Drug (n = 138)	At Least 2 Antithrombotic Drugs (n = 118)	p Value
Recanalization	112/138 (81)	100/117 (85)	0.454
Early neurological improvement	31/67 (46)	32/68 (47)	1
90-day favorable outcome	77/136 (57)	70/118 (59)	0.758
90-day mortality	10/136 (7)	14/118 (12)	0.312
Symptomatic Hemorrhagic complications	5/137 (4)	8/118 (7)	0.397

Values are n/N (%). Recanalization was defined as mTICI grade 2B or 3 at the end of thrombectomy. Early neurological improvement defined as NIHSS score 0 or 1 at 24 h or a decrease of 4 or more points in NIHSS score at 24 h. Favorable outcome was defined as an mRS score of 2 or less. Symptomatic hemorrhagic complications were defined as any parenchymal hematoma, subarachnoid hemorrhage, or intraventricular hemorrhage associated with worsening of the NIHSS score of 4 points or more according to the ECASS-2 criteria.

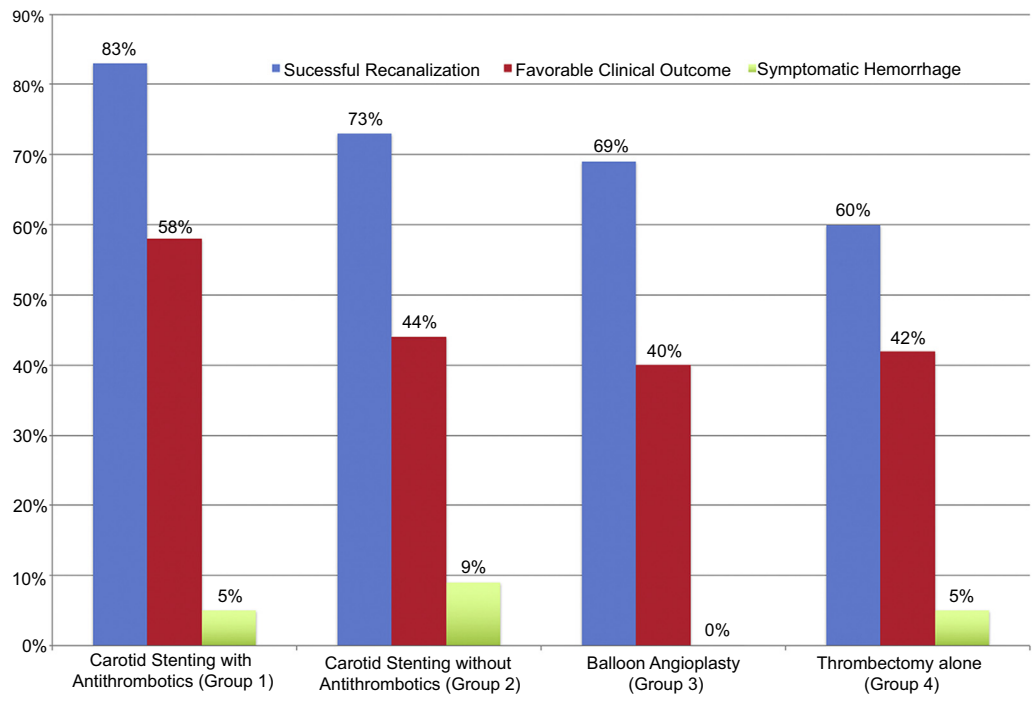
Abbreviations as in Tables 1 and 2.

on the basis of the technical aspects of the intervention and with regard to potential complications.

ACUTE STENTING OF THE EXTRACRANIAL ICA LESION AND INTRACRANIAL THROMBECTOMY. The predominant pathophysiologic process involved in acute occlusion of the extracranial ICA is ruptured atherosclerotic plaque and superimposed thrombus. Because of its similarity to acute occlusion of the coronary arteries, a similar treatment approach is often applied: acute stent implantation (16,17), an approach that has been shown to yield good angiographic and clinical results (3,18). Acute stenting and angioplasty of the extracranial lesion offers 2 obvious advantages: 1) placement of the stent directly treats the extracranial lesion (**Figure 2**); and 2) it facilitates passage of a guiding sheath through the lesion to access the intracranial occlusion. The main disadvantage, however, is the potential risk for acute stent thrombosis (19).

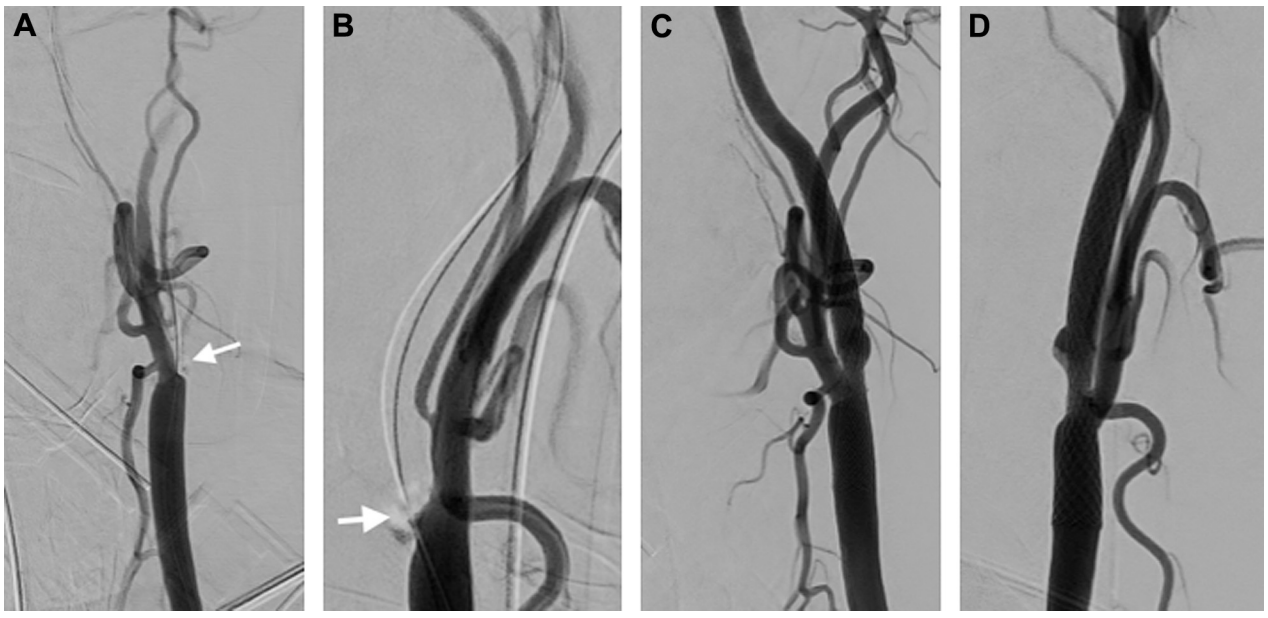
BALLOON ANGIOPLASTY OF THE EXTRACRANIAL ICA LESION AND INTRACRANIAL THROMBECTOMY. Balloon dilatation of the ICA stenosis to pass the guiding sheath and perform intracranial thrombectomy, while treating the stenosis in a separate second step, represents a more conservative therapeutic approach. The rationale for this method is to avoid administration of antithrombotic medication to reduce the risk for intracranial hemorrhage, which is a specific and highly concerning matter to brain ischemia (10). Despite this advantage, a potential problem with this approach is new thrombus formation (20,21) which

FIGURE 1 Outcomes and Hemorrhage Rates per Therapeutic Group



Angiographic outcomes, clinical outcomes, and symptomatic hemorrhage rates per therapeutic group.

FIGURE 2 Acute Stenting of the Extracranial Internal Carotid Artery



Revascularization of the extracranial internal carotid artery (ICA) with stent implantation. **(A, B)** Acute atherosclerotic occlusion shortly beyond the origin of the ICA **(white arrows)**. **(C, D)** After stent placement and balloon angioplasty, normal ICA outflow is visible.

results in more intracranial thrombus embolization during EVT. This may explain the lower rate of successful recanalization and lower proportion of favorable clinical outcomes observed with this treatment regimen.

INTRACRANIAL THROMBECTOMY WITHOUT TREATMENT OF THE EXTRACRANIAL ICA LESION. This approach (treatment 4) was used in 108 of 482 patients in this study. However, the rates of successful recanalization and good clinical outcome were significantly lower compared with treatment 1. Because intracranial occlusion is the principal cause of symptoms, this approach aims to achieve intracranial recanalization, leaving the extracranial lesion untreated to avoid requisite antithrombotic medication. Even in scenarios with complete ICA occlusion, if the circle of Willis is present, the recanalized intracranial artery can stay open. In addition, this procedure may be performed more quickly than stenting and thrombectomy, because it ignores treatment of the extracranial carotid lesion (22). However, this approach is technically challenging (passing the occlusion or stenosis with a 6-F sheath or catheter is rather difficult) and fails to reduce the risk for embolization, which may explain its lower success rate. Moreover, the success rate for reperfusion was significantly lower for patients receiving treatment 4 compared with patients who had the ICA lesion treated (combined groups 1, 2, and 3), suggesting that the ICA lesion should be always treated.

ACUTE ANTITHROMBOTIC MEDICATION. The antithrombotic regimen is a major concern in the EVT of tandem lesions, especially with acute carotid stenting. If patients have already received IV tPA, additional antithrombotic agents may increase the risk for hemorrhagic complications (23). However, without antithrombotic drugs, acute stent thrombosis can occur (19). From the published research on coronary interventions, we know that most thrombotic events occur within hours of the acute stenting procedure. Therefore, antithrombotic drugs must be administered during the intervention (24,25). Our study showed that administering 1 or even 2 antithrombotic drugs was associated with a low risk for intracranial hemorrhage. Moreover, treatment 1 (i.e., with antithrombotic agents) had the highest rate of intracranial recanalization (83%) and the highest rate of favorable clinical outcomes (58%), whereas the same treatment without antithrombotic drugs yielded a lower rate of favorable clinical outcomes (44%), without any benefit regarding the rate of sICH (9%). These results suggest that the administration of

antithrombotic drugs might be a reasonable strategy if acute carotid stenting is performed.

Despite these favorable results, we are unable to recommend a specific protocol, because the different participating centers used rather heterogeneous antithrombotic regimes, using IV aspirin, IV glycoprotein IIb/IIIa receptor antagonist, clopidogrel, and heparin in the acute phase. Even for primary percutaneous coronary interventions, the optimal medical treatment combination remains a matter of debate (26), and many challenges need to be overcome to determine the optimal benefit/risk ratio.

STUDY LIMITATIONS. Although the large sample size allowed comparison of different treatment strategies for tandem lesions in patients with AIS, our study had several limitations, such as its retrospective, noncontrolled design, the relatively small sample sizes of groups 2 and 3, the lack of data regarding the use of embolic protection, and the lack of a core laboratory. In addition, although all centers had high levels of experience, they used individual selection protocols (introducing possible selection bias) and heterogeneous antithrombotic strategies. Although multiple imputation was performed to handle missing data in some model covariates, we cannot exclude that nonrandom missing data could have introduced a degree of bias in calculated estimands.

CONCLUSIONS

Our study showed that the combination of acute stenting of the extracranial ICA lesion with antithrombotic agents and intracranial thrombectomy may be the best treatment strategy to treat tandem lesions in patients with AIS. This approach yielded the highest overall recanalization rates and a high rate of favorable clinical outcomes. Administration of antithrombotic drugs, even in combination with IV tPA, did not increase the rate of sICH. Further prospective and randomized trials are needed to test whether this technique is indeed the best treatment strategy for tandem lesions. In addition, future studies should focus on establishing an optimal antithrombotic regimen (Online Appendix).

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PERSPECTIVES

WHAT IS KNOWN? EVT of tandem lesions in AIS is more beneficial than the standard treatment using IV thrombolysis. However, there is currently no consensus regarding the ideal interventional strategy.

WHAT IS NEW? Carotid artery stenting with antithrombotic therapy and intracranial thrombectomy for treatment of tandem lesions shows higher recanalization rates compared with other treatment strategies.

WHAT IS NEXT? Because the optimal antithrombotic regimen is not known, clinical studies comparing different antithrombotic regimes in treatment of tandem lesions are warranted.

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KEY WORDS acute stroke, carotid stenting, recanalization, thrombectomy

APPENDIX For a list of TITAN trial investigators, please see the online version of this paper.