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Sørensen, Mads M.; Leslie-Mazwi, Thabele M.; Jensen, Jonas; Valentin, Jan B.; Simonsen, Claus Z.

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ORIGINAL RESEARCH

Endovascular Therapy of Tandem Occlusions: Baseline Characteristics and Outcomes Compared With Intracranial Occlusion

Mads M. Sørensen; Thabele M. Leslie-Mazwi, MD; Jonas Jensen, MD, PhD; Jan B. Valentin;
Claus Z. Simonsen, MD, PhD 

BACKGROUND: Endovascular therapy is highly effective in stroke caused by large vessel occlusion. Guidelines support treatment in case of occlusion of the intracranial internal carotid artery or the first segment of the middle cerebral artery. We aimed to examine baseline characteristics and outcome of patients who underwent endovascular therapy for tandem occlusions.

METHODS: We conducted a retrospective study of patients who underwent endovascular therapy of tandem occlusion or occlusion of intracranial internal carotid artery/first segment of the middle cerebral artery between May 2015 and December 2019. Univariate comparisons of baseline characteristics and outcome (favorable functional outcome 90-days after treatment and mortality) were performed. We used inverse-probability-of-treatment-weights to adjust for confounders.

RESULTS: We compared 167 patients with tandem occlusion and 414 with intracranial occlusions. Patients with tandem occlusion were younger (69 years [interquartile range: 59.25–76] versus 74 [interquartile range: 64–81]; $P = 0.0002$), male (64.7% versus 51.4%; $P = 0.004$), more frequently active smokers (42.5% versus 25.6%; $P = 0.0001$), and less frequently subject to atrial fibrillation (18.6% versus 41.3%; $P < 0.0001$). No significant differences were seen in the rate of 90-day good outcome (49.1% versus 51.0%; $P = 0.68$) or mortality (16.8% versus 18.1%; $P = 0.70$). This was also true after adjustment (relative risk for poor outcome 0.86 [95% CI: 0.72–1.05]). More proximal occlusions resulted in worse outcome in both tandem and intracranial occlusions.

CONCLUSION: Patients with tandem occlusion were more frequently younger, male smokers without atrial fibrillation illustrating the different risk factors underlying these strokes. Benefit from treatment was similar between groups, supporting endovascular therapy in tandem occlusions.

Key Words: acute ischemic stroke ■ endovascular thrombectomy ■ tandem occlusion

Guidelines strongly support treatment with endovascular therapy (EVT) in case of occlusion of the intracranial segment of the internal carotid artery (ICA-T) or the first segment of the mid-

dle cerebral artery (M1). Tandem occlusion refers to occlusion in the cervical region with distal migration of clot producing additional occlusion in the intracranial portion of the vessel. This can either be in the ICA-T

Correspondence to: Claus Z. Simonsen, Department of Neurology, Aarhus University Hospital, 8200 Aarhus, Denmark. E-mail: clasim@rm.dk

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or M1 segment or more distal in the middle cerebral artery. Guidelines stipulate that treatment of tandem occlusions may be reasonable.¹

Randomized trials^{2–4} indicate that patients with tandem occlusions benefit from EVT similarly to patients without extracranial carotid occlusions.⁵ Studies have examined prognostic factors for patients with tandem occlusion, finding similarities to patients with intracranial lesions^{6,7} and even comparable outcome with patients undergoing therapy for intracranial occlusions of the ICA-T or M1 that adheres to best evidence (“guideline occlusion”). However, the approach to tandem occlusions is debated.^{7–9}

In this study, we aimed to compare baseline characteristics and outcome of stroke patients undergoing EVT of tandem occlusions and anterior circulation intracranial occlusions (ICA-T or M1) to inform etiological considerations (atherosclerosis or cardiac emboli) and assess outcomes.

METHODS

Data Collection

The data that support the findings of this study is available on reasonable request. The STROBE guidelines have been followed. We retrospectively reviewed patients who underwent EVT at our center between May 1, 2015 and December 31, 2019. Data were obtained from a prospectively maintained database. It included 879 patients of which 11 patients had no documented 90-day follow-up and were excluded. Of the remaining patients, 287 had occlusions of other vessels including M2 occlusions and tandem occlusion with M2 occlusion, while 414 had occlusion of the ICA-T or M1 (“guideline occlusions”). The remaining 167 patients were admitted with tandem occlusions. Of these, 77 had occlusion of the ICA alone. We compared the patients with isolated ICA occlusions to the “true” tandem occlusions and found them very similar (see Supplementary material Table S1). Given similar implications for etiology and treatment decisions, the patients with isolated ICA occlusions were therefore included in the tandem group (see Figure 1 for details).

Clinical Assessment

We extracted data on baseline characteristics including but not limited to age, sex, National Institute of Health Stroke Scale score at presentation, comorbidities (hypertension, alcohol, active and previous smoking, diabetes, atrial fibrillation [AF], history of stroke, or myocardial infarction), administration of IV thrombolysis, and location of the intracranial occlusion. Symptomatic intracerebral hemorrhage was defined as a type 2 parenchymal hemorrhage on follow-up scan

Nonstandard Abbreviations and Acronyms

EVT	endovascular therapy
ICA-T	intracranial internal carotid artery
M1	first segment of the middle cerebral artery

CLINICAL PERSPECTIVE

- Comorbidities differ among patients with tandem stenosis and intracranial occlusion.
- Patients with tandem stenosis are often younger males who are actively smoking, while intracranial occlusions are often older with atrial fibrillation.
- Outcomes are similar after endovascular therapy.

combined with an increase of 4 point or more on the 24-hour National Institute of Health Stroke Scale.

For outcome, modified Rankin scale score 90 days after EVT was prospectively acquired by in-person clinic visit or by telephone contact (only if the patient was unable to travel). A good outcome was defined as modified Rankin scale 0–2 (living independently). A secondary outcome was mortality rates (see Table 1). In addition, we compared outcomes according to the location of the intracranial occlusion (see Table 2).

Endovascular Therapy

For M1/ICA-T occlusion, patients were treated per standard protocols with either a stent retriever and/or aspiration device. Antiplatelet therapy was started after a 24-hour scan excluded significant hemorrhage. For patients with confirmed AF, antiplatelet therapy was discontinued after 3 to 12 days (depending on infarct size) and anticoagulation therapy was commenced.

In the tandem group, balloon angioplasty was performed when necessary to advance through the stenosis. The intracranial lesion was treated as above. At the discretion of the interventionalist, a stent was placed after treatment of the intracranial lesion. In case of stent placement or angioplasty, aspirin was given periprocedurally and clopidogrel was started after a 24-hour scan excluded significant hemorrhage. Dual antiplatelet (aspirin+clopidogrel) was continued for a total of 3 months after which typically aspirin was stopped. There was no use of intravenous GP IIb/IIIa inhibitors.

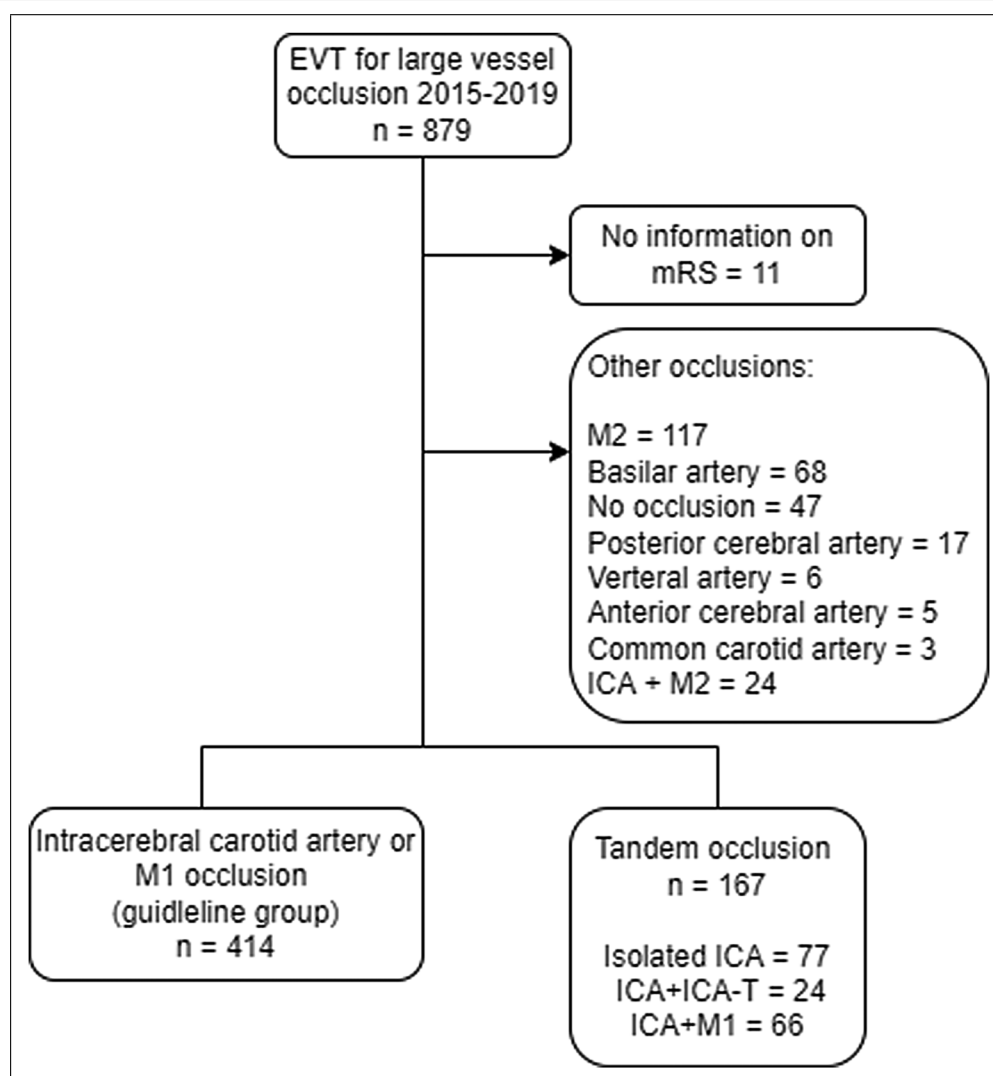


Figure 1. Flowchart describing the 879 patients treated with endovascular therapy.

Statistical Methodology/Analysis

Standard descriptive statistics was used to present baseline characteristics and outcomes. Categorical measures were reported with numbers and rates (%) and continuous measures with medians or means. For the univariate comparisons between the 2 groups, we applied Pearson chi-square or Mann-Whitney U test where appropriate. Subsequently, we performed a Poisson-regression analysis¹⁰ with robust variance estimator to estimate the relative risk¹¹ between the different lesion locations/types of occlusions on mortality and bad functional outcome. We adjusted for potential confounding using inverse-probability-of-treatment-weights and presented the results with 95% CIs. Obvious risk factors were chosen as adjustment parameters and constituted medical history (hypertension, diabetes, smoking status, hypercholesterolemia,

AF, previous myocardial infarction, and previous stroke), as well as stroke severity, age, and sex. The statistical analysis was carried out using STATA version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX, StataCorp LLC.) A *P*-value of less than 0.05 was considered to be statistically significant.

Under Danish national law, registry-based studies require no ethical approval or patient consent.

RESULTS

Between May 2015 and December 2019, a total of 414 patients with available 90-day modified Rankin scale scores underwent EVT for ICA-T or M1 occlusions and 167 for comparable tandem occlusions (see Figure 1).

Table 1. Baseline Characteristics and Outcomes of Patients With Tandem or Intracranial Occlusion

	Tandem (n = 167)	ICA-T/M1 occlusion (n = 414)	P-value
Male sex	108 = 64.7%	213 = 51.4%	0.004
Age (median)	69 (59.25–76)	74 (63–81)	0.0002
Prestroke dependent (mRS>2)	6 = 3.6%	22 = 5.3%	0.38
NIHSS	16 (12–21)	18 (13–22)	0.054
Hypertension	101 = 60.5%	210 = 50.7%	0.033
Diabetes	21 = 12.6%	49 = 11.8%	0.80
Smoker, active	71 = 42.5%	106 = 25.6%	0.0001
Smoker, previous	50 = 29.9%	123 = 29.7%	0.96
Hypercholesterolemia	135 = 80.8%	304 = 73.4%	0.060
AF	31 = 18.6%	171 = 41.3%	<0.0001
Previous MI	17 = 10.2%	44 = 10.6%	0.87
Previous stroke	25 = 15.0%	74 = 17.9%	0.40
tPA given	100 = 59.9%	232 = 56.0 %	0.40
Onset to groin puncture (minutes)	233 (162–330)	210.0 (145–317)	0.15
Treated under general anesthesia	80 = 47.9%	155 = 37.4%	0.02
Symptomatic ICH	4 = 2.4%	8 = 1.9%	0.72
Perforation	1 = 0.6%	7 = 1.7%	0.31
Successful reperfusion (mTICI 2b–3)	132 = 79.0%	358 = 86.5%	0.026
Independent poststroke (mRS 0–2)	82 = 49.1%	211 = 51.0%	0.68
Mortality	28 = 16.8%	75 = 18.1%	0.70
Independent poststroke (mRS 0–2), adj.	72 = 44.4%	213 = 51.3%	0.18
Mortality, adj.	35 = 21.5%	70 = 17.0%	0.33

Adj., adjusted for medical history (hypertension, diabetes, smoking status, hypercholesterolemia, AF, previous MI, and previous stroke) as well as stroke severity, age, and sex; M1, first branch of the middle cerebral artery. AF indicates atrial fibrillation; ICA-T, intracranial internal carotid artery; ICH, intracerebral hemorrhage; MI, myocardial infarction; mRS, modified Rankin score; mTICI, modified thrombolysis in cerebral ischemia; NIHSS, National Institute of Health Stroke Scale; and tPA, tissue plasminogen activator.

Table 2. Patient Outcome in Relation to Level of Vascular Occlusion

Lesion location		Good outcome, 90-day mRS 0–2	Mortality
Guideline occlusion (n = 414)	ICA-T (n = 73)	24 = 32.9%	23 = 31.5%
	M1 (n = 341)	187 = 54.8%	52 = 15.2%
Tandem occlusions (n = 167)	Carotid+ICA-T (n = 24)	8 = 33.3%	5 = 20.8%
	Carotid+M1 (n = 66)	35 = 53.0%	8 = 12.1%
	Carotid occlusion alone (n = 77)	39 = 50.6%	15 = 19.5%

M1, first branch of middle cerebral artery. ICA-T indicates intracranial internal carotid artery; and mRS, modified Rankin scale.

Patients with tandem occlusions differed significantly from patients with guideline occlusions in being younger (69 years, interquartile range: 59.25–76 versus 74 years, interquartile range: 63–81; $P = 0.0002$) and more often male (64.7% versus 51.4%; $P = 0.004$).

Regarding comorbidities, patients with tandem occlusion were more frequently active smokers (42.5% versus 25.6%; $P = 0.0001$) while patients with guideline occlusion more frequently had AF (41.3% versus 18.6%; $P < 0.0001$). Patients with tandem occlusion more often had hypertension (60.5% versus 50.7%; $P = 0.033$). The remaining variables of the medical history including diabetes, hypercholesterolemia,

being a former smoker, history of stroke or myocardial infarction, thrombolytic administration, and time to groin puncture did not differ significantly between the 2 groups. Patients with tandem occlusion were more often treated under general anesthesia (47.9% versus 37.4%; $P = 0.02$). Successful reperfusion was more often achieved for those with guideline occlusions (86.5% versus 79.0%; $P = 0.026$). The various reperfusion grades in the 2 groups are presented in Figure 2.

Crude analyses revealed that a good outcome was achieved in 49.1% of tandem occlusion patients (reference) and in 51.0% of patients with a guideline occlusion with a relative risk of a poor outcome: 0.96

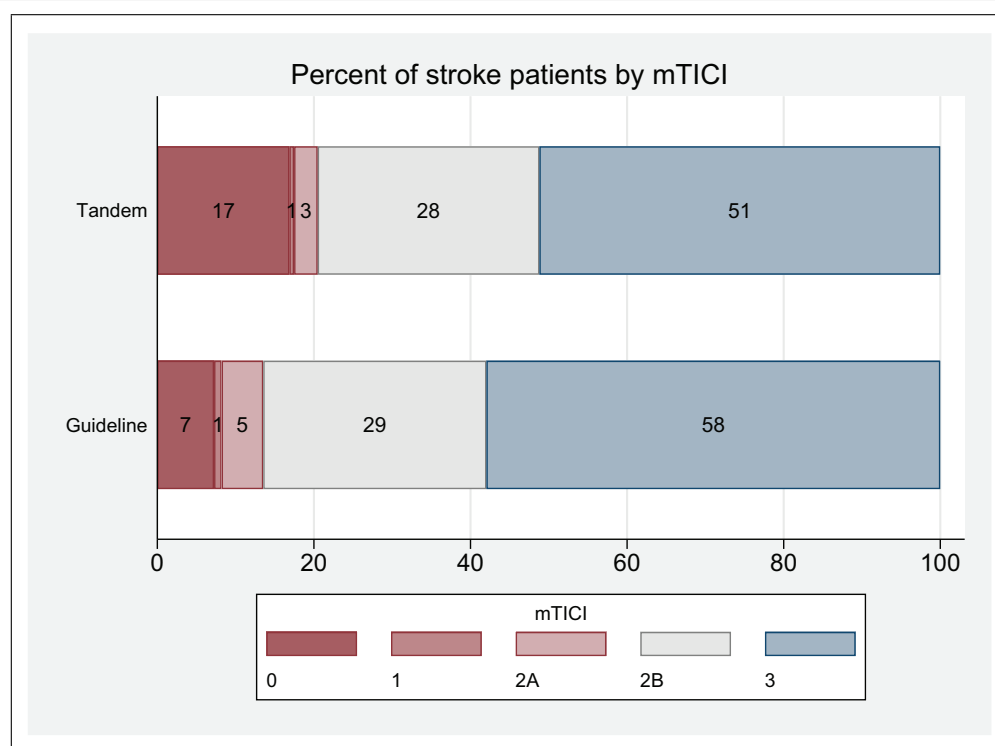


Figure 2. Distribution of the reperfusion scores in the 2 groups.

(95%CI: 0.81–1.15). Mortality at 90-days was similar (Table 1) with a risk ratio of 1.08 (95%CI: 0.73–1.61). The modified Rankin scale outcomes in the 2 groups are presented in Figure 3.

After adjustment, the results on mortality and poor functional outcome both pointed toward beneficial effect of ICA-T/M1 occlusion, however, there was still no statistically significant difference in either outcome between tandem occlusions (reference) and guideline occlusions (see Table 1 for adjusted proportions) with the relative risk of a poor outcome being 0.86, (95%CI: 0.72–1.05) and relative risk of death being 0.79 (95%CI: 0.50–1.23). Balance diagnostics of the weighted analyses are provided in Supplementary material Table S2.

More proximal occlusions resulted in worse outcome; only 32.9% of the ICA-T occlusions had a good outcome compared with 54.8% of the M1 occlusion. The same pattern was found for tandem occlusions (see Table 2). Interestingly, the patients with isolated cervical occlusions of the ICA (for whom optimal treatment is not yet established) had a good outcome rate of 50.6%, making them comparable with the EVT group as a whole.

Procedure time as measured in minutes from groin puncture to reperfusion was longer for the tandem group (39 minutes [interquartile range: 24–61.75] versus 27 minutes [interquartile range: 17–45]; $P < 0.0001$).

Table 3 illustrates the various methods and procedure times. In the guideline group, 27 patients received an angioplasty procedure, indicating coexisting atherosclerotic disease.

DISCUSSION

In the present study, we evaluated clinical outcome and baseline characteristics of patients undergoing treatment of tandem occlusion or intracranial occlusion of ICA-T/M1. The main findings were that tandem occlusion is more frequently seen in younger, male smokers, while guideline occlusions are more often seen in patients with AF, but that both groups of patients achieved comparable outcomes. Patients with isolated cervical ICA occlusions benefitted equally from treatment.

Large vessel occlusion develop acutely through different mechanisms: superimposed thrombosis in patients with intracranial atherosclerosis, artery-to-artery embolism (from proximal vasculature), cardiac embolism, or cryptogenic causes.¹² The pathophysiology of tandem occlusion differs from that of the intracranial occlusions. Intracranial occlusions are commonly caused by embolization from other sources (eg, cardio embolization due to AF). For tandem

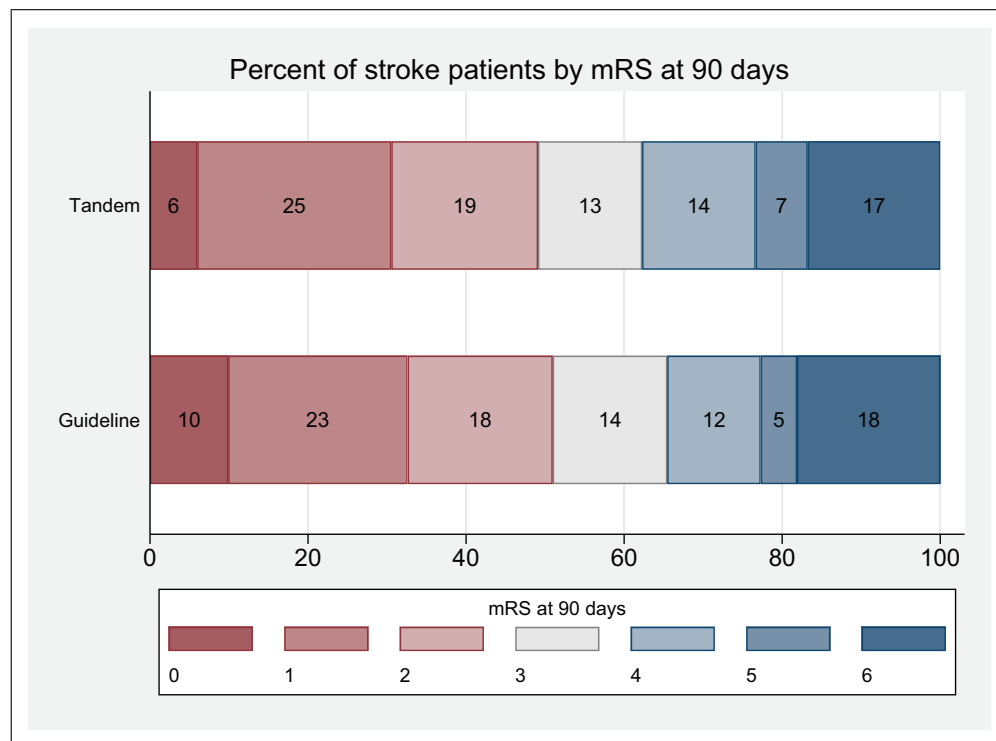


Figure 3. Grotta bars presenting the outcomes in the 2 groups by modified Rankin scores.

Table 3. Technical Details of the Thrombectomy Procedure

	Tandem (n = 167)	M1/ICA-T (n = 414)	
Extracranial stent placed	81 (48.5%)	32 (7.7%)	<0.0001
Stent retriever alone	35 (21.0%)	148 (35.7%)	0.0005
Aspiration alone	45 (26.9%)	116 (28.0%)	0.79
Stent retriever and aspiration	47 (28.1%)	110 (26.6%)	0.70
Groin puncture to reperfusion (min)	39 (24–61.75) N = 131	27 (17–45) N = 353	<0.0001

M1, first branch of middle cerebral artery. ICA-T indicates intracerebral internal carotid artery.

occlusions, atherothrombosis can cause occlusion and hemodynamic compromise but more often atherosclerotic disease of the extracranial carotid artery causes embolization to intracranial arteries (“artery-to-artery embolization”).^{13,14} It has been difficult historically to link any specific risk factors to etiologies of stroke.¹⁵

In this study, we found that patients with tandem occlusion are predominantly younger males who actively smoked. Smoking is accepted as an important risk factor of atherosclerosis with newer data suggesting an effect on primarily extracranial vessels. A large prospective study of 2864 patients identified a dose–response relationship between smoking and extracranial atherosclerotic stenosis (odds ratio 1.47; $P < 0.01$) but not intracranial atherosclerosis.¹⁶ This trend has been identified in both Chinese and Caucasian populations,^{17–19} with male sex and hypertension identified as independent additional risk factors. In

our study, hypertension just reached significance, being present in 60.5% of patients with tandem occlusion and 50.7% in guideline occlusion. In most previous observational studies, the same pattern has been found, with reports of significantly higher prevalence of male sex in patients with tandem occlusion (79% versus 51%)^{7,9} and active smokers (51% versus 32%)^{7,9} compared with intracranial occlusions.

Data from a post hoc analysis of the ESCAPE trial found subjects of tandem occlusion to be younger, predominantly male with higher prevalence of diabetes (37% versus 20%) and smoking (33% versus 18%) when compared with patients with intracranial occlusions.²⁰ Also, in the WAKE-UP study, smoking was seen more commonly in large artery disease²¹ where smokers also were younger and less often had AF. Interestingly, there is no overrepresentation of tandem occlusion among previous smokers, indicating

that it is active smoking that likely causes plaque activation.

As for patients with stroke caused by intracranial occlusions, the prevalence of AF was notable. AF is a well-known risk factor for cardio-embolic events and produces a 5-fold increase in incidence of stroke.²² The prevalence of AF increases with advancing age, which in itself promotes the risk of stroke.²³

Whether female sex modifies stroke risk from AF remains a point of debate. The increased risk seen in women could be due to insufficient adjustment for age.²⁴ An alternate argument is that when risk factors are present, women are considered at higher stroke risk than men with similar risk profile.^{25,26} A Danish nationwide cohort study found AF in female patients aged >75 to be associated with a 20% increased stroke risk.²⁷ Much points toward AF posing a substantial risk of stroke in woman. In our population, AF was seen in 41% of all the women and in 28% of all men ($P = 0.0012$).

Generally, age-specific stroke rates are higher in men. However, due to sex-differences in the incidence of stroke attributable to AF and a prevalence of AF of over 40% of patients with intracranial occlusions, this occlusion group is noted for advanced age and equal sex distribution. AF and intracranial occlusion have been described in previous reports of observational studies comparing tandem occlusion with intracranial occlusions, finding significantly different prevalence of AF (13% versus 56% in tandem versus intracranial occlusion, respectively).^{7–9} A meta-analysis evaluating sex disparities in stroke found women to suffer more cardioembolic strokes and men more atherothrombotic strokes.²⁸

Comparable to our findings, published retrospective studies found comparable outcomes between tandem occlusions and intracranial occlusions.^{7–9} Good clinical outcome was achieved in 55% of the tandem occlusion cases and 54% of cases with intracranial occlusion and mortality rates of 13% and 10% in tandem versus intracranial groups, respectively. The ESCAPE and MR CLEAN trials found no difference when comparing outcome and mortality rates in tandem and nontandem patients.^{20,29}

Our subgroups analysis of lesion sites revealed that occlusion of distal intracranial segments was associated with better outcome in both occlusion groups. In the group with guideline occlusions, good outcome was seen twice as often in the group with M1 occlusion, while mortality was halved compared with patients with ICA-T occlusion. The same pattern was seen in tandem occlusions indicating that the determination of the prognosis is related to the location of the intracranial occlusion and not the cervical one. That the rate of good outcome was lower with more proximal occlu-

sion, has been described previously.^{30,31} The patients with isolated ICA occlusions had comparable good outcome.

Procedure time was generally longer for the tandem occlusion patients where catheter maneuvering through the cervical region was more difficult and a stent might need to be placed. This was also reflected by more patients requiring general anesthesia. Whether patients with tandem occlusions need an acute stent at the carotid stenosis is debated,³² and this equipoise is reflected in our findings, with 48.5% receiving a stent. Selection of reperfusion devices was at the discretion of the neurointerventionalist, but it appears that the stent retriever was used less often in case of a tandem stenosis. Our findings are consistent with another report identifying a similar pattern.³³

Our study has several limitations, the retrospective, noncontrolled design of this single-center study limits its level of evidence. Beyond that we would highlight the limitations of our data set; infarct size and collateral flow were not assessed but would have been useful given their association with clinical outcome. Strengths of this study include homogeneity of treatment, expertise, and workflow within the same center, and the high rate of detailed 90-day clinical follow-up.

CONCLUSION

Patients with tandem occlusions are more frequently male, active smokers that less often have AF. These findings point to accelerated extracranial atherosclerosis as a dominant mechanism in tandem occlusion patients. Despite different pathophysiology and uncertainty on the best approach to the cervical lesion in tandem occlusion patients, treatment seems to benefit both tandem and isolated intracranial occlusion patients equally and should be pursued aggressively in tandem occlusion cases.

ARTICLE INFORMATION

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Affiliations

Department of Neurology, Aarhus University Hospital, Aarhus, Denmark (M.M.S., C.Z.S.); Department of Neurology, University of Washington, Seattle, WA (T.M.L.-M.); Neuroradiology, Aarhus University Hospital, Aarhus, Denmark (J.J.); Department of Clinical Medicine, Aalborg University and Aalborg University Hospital, Aalborg, Denmark (J.B.V.); Department of Clinical Medicine, Aarhus University, Aarhus, Denmark (C.Z.S.)

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Supplemental Materials

Supporting Information
Tables S1 and S2

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