Artery occlusion independently predicts unfavorable outcome in cervical artery dissection

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Abstract

Objective

To assess the impact of dissected artery occlusion (DAO) on functional outcome and complications in patients with cervical artery dissection (CeAD).

Methods

We analyzed combined individual patient data from 3 multicenter cohorts of consecutive patients with CeAD (the Cervical Artery Dissection and Ischemic Stroke Patients [CADISP]-Plus consortium dataset). Patients with data on DAO and functional outcome were included. We compared patients with DAO to those without DAO. Primary outcome was favorable functional outcome (i.e., modified Rankin Scale [mRS] score 0–1) measured 3–6 months from baseline. Secondary outcomes included delayed cerebral ischemia, major hemorrhage, recurrent CeAD, and death. We performed univariate and multivariable binary logistic regression analyses and calculated odds ratios (OR) with 95% confidence intervals (CI), with adjustment for potential confounders.

Results

Of 2,148 patients (median age 45 years [interquartile range (IQR) 38–52], 43.6% women), 728 (33.9%) had DAO. Patients with DAO more frequently presented with cerebral ischemia (84.6% vs 58.5%, $p < 0.001$). Patients with DAO were less likely to have favorable outcome when compared to patients without DAO (mRS 0–1: 59.6% vs 80.1%, $p_{\text{unadjusted}} < 0.001$). After adjustment for age, sex, and initial stroke severity, DAO was independently associated with less favorable outcome (mRS 0–1: OR 0.65, CI 0.50–0.84, $p = 0.001$). Delayed cerebral ischemia occurred more frequently in patients with DAO than in patients without DAO (4.5% vs 2.9%, $p = 0.059$).

Conclusion

DAO independently predicts less favorable functional outcome in patients with CeAD. Further research on vessel patency, collateral status and effects of revascularization therapies particularly in patients with DAO is warranted.

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Glossary

CADISP = Cervical Artery Dissection and Ischemic Stroke Patients; **CeAD** = cervical artery dissection; **CI** = confidence interval; **CIE** = cerebral ischemic events; **DAO** = dissected artery occlusion; **EVT** = endovascular therapy; **ICAD** = internal carotid artery dissection; **IQR** = interquartile range; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **VAD** = vertebral artery dissection.

Cervical artery dissection (CeAD) is a major cause of ischemic stroke in young adults.¹ Mural hematoma in the cervical portion of the internal carotid or vertebral artery is a hallmark of CeAD. Its enlargement or local thrombosis at the site of dissection can lead to dissected artery occlusion (DAO), which was found in about one-third of patients with CeAD in prior studies.^{2–5} In contrast to the reported prognostic significance of Horner syndrome or pulsatile tinnitus as local signs of CeAD,^{5,6} little is known about the prognostic importance of DAO in CeAD. One observational study suggests worse outcome for patients with CeAD with DAO of the internal carotid artery compared to patients with artery occlusion due to atherothrombotic disease.⁷ Another study identified DAO as a determinant of delayed stroke in patients with CeAD.⁸ However, due to scarcity of comparisons of patients with CeAD with DAO vs those without DAO, it remains to be shown whether DAO independently determines outcome in CeAD.

In this study, we aimed to determine the effect of DAO on functional outcome in patients with CeAD based on analyses of the dataset of the Cervical Artery Dissection and Ischemic Stroke Patients (CADISP)-Plus consortium.^{9,10}

Methods

Study population and data collection

The present study is based on data derived from the dataset of the multicenter CADISP-Plus consortium. This dataset currently comprises individual patient data of 2,526 patients with CeAD from 3 large clinical CeAD patient cohorts: (1) the CADISP-1 clinical study (n = 983), which recruited predominantly in European countries¹¹; the CADISP-2 cohort (US centers, n = 411 patients); and the Paris-Lariboisière/Zurich/Bern CeAD registry (n = 1,132 patients). In the current study, only data from patients with data on outcome and presence or absence of DAO at baseline were included. The structure and methods of the CADISP-Plus consortium have been described in prior research.^{10–12} In brief, patients with CeAD were evaluated and included in the cohorts at neurology departments mostly of tertiary care centers. Iatrogenic dissections were excluded and patients were evaluated according to standardized protocols.^{9,12} In a previous study, meta-analyses of separate data of these 3 cohorts showed homogeneity of patient characteristics across cohorts, allowing pooling of data for further individual patient data analyses.¹⁰ All sites contributing data to these clinical CeAD patient cohorts

applied the same widely accepted diagnostic CeAD criteria and definitions of key variables described in prior research.^{10,12} In brief, diagnostic criteria of CeAD were as follows (at least one): presence of a mural hematoma, aneurysmal dilation, long tapering stenosis, intimal flap, double lumen, or occlusion situated >2 cm above the carotid bifurcation revealing an aneurysmal dilation or a long tapering stenosis after recanalization.^{1,11} These criteria were applied for diagnosis of internal carotid artery dissection (ICAD) or vertebral artery dissection (VAD) if suitable and had to be visualized by CT, MRI, or digital subtraction angiography.¹²

Study variables and patient clinical and radiologic characteristics

For the present study, the following data were derived from the CADISP-Plus dataset: (1) demographic data (age, sex); (2) site of dissection (internal carotid artery or vertebral artery); (3) baseline clinical symptoms (cerebral ischemic events [CIE], i.e., TIA or ischemic stroke, including stroke severity as measured by the NIH Stroke Scale [NIHSS]; Horner syndrome; pulsatile tinnitus; cervical pain; or headache); (4) presence or absence of putative CeAD risk factors (preceding mechanical trigger event); (5) history of migraine; and (6) vascular risk factors (hypertension, hypercholesterolemia, or diabetes). The definitions of these variables were described previously.^{10–12} Presence or absence of DAO (in ICAD or VAD) at first imaging assessment was determined by individual site investigators and was derived from the CADISP-Plus database for the present analysis. No central adjudication of these findings was performed. All patients with CeAD included in the CADISP-Plus database had imaging-confirmed CeAD; however, there were no standardized (timing or modality) vessel imaging protocols to identify DAO. Performance of acute recanalization therapy (i.e., IV thrombolysis or endovascular therapy [EVT]; i.e., intra-arterial thrombolysis, mechanical thrombectomy, or stenting) as well as choice of antithrombotic therapy (i.e., antiplatelets or anticoagulants) were left to the discretion of the treating physicians and were derived from the database for the present analysis.

Outcome

Functional outcome was assessed between 3 and 6 months during outpatient visit or telephone interview using the modified Rankin Scale (mRS). In the present study, favorable outcome was defined as an mRS score of 0 or 1 (primary outcome) as done in prior research.⁵ Data on (1) occurrence of CIE during follow-up, (2) recurrent CeAD, (3) major

hemorrhage (intracranial or extracranial), and (4) death during follow-up were recorded (secondary outcomes).

Statistical analyses

We compared patients with CeAD with DAO at baseline to those without. We compared baseline characteristics and clinical data between both groups using the χ^2 test or the Fisher exact test if appropriate for categorical variables and the Mann-Whitney test for continuous variables.

Primary outcome analyses

To assess the impact of DAO on functional outcome, we first performed univariate binary logistic regression analyses. Based on results from the comparisons of baseline characteristics and prior research on known predictors of outcome,^{13,14} we performed multivariable binary logistic regression analyses including the following covariates and favorable outcome (i.e., mRS 0–1) as outcome measures: age, sex, stroke severity as measured by the NIHSS (in patients with CIE), and presence of DAO.

In secondary analyses, we included the following additional covariates in the primary multivariable logistic regression model: occurrence of (1) CIE, (2) recurrent CeAD, or (3) major intracranial or extracranial hemorrhage during follow-up.

In a third step, we performed the following sensitivity analyses using favorable outcome as outcome measure: (1) multivariable logistic regression as performed in the primary outcome analyses separately in patients with ICAD or VAD; (2) including presence of Horner syndrome and tinnitus, both known to predict favorable outcome in patients with CeAD,^{5,6} in our primary multivariable logistic regression model in patients with ICAD; and (3) separate multivariable logistic regression analyses including age, sex, and DAO as covariates in patients with (1) no signs of cerebral ischemia, (2) TIA, or (3) ischemic stroke at baseline.

All statistical analyses were performed using SPSS version 25 (IBM; Armonk, NY). A *p* value <0.05 was considered statistically significant in all analyses.

Data availability

Datasets generated or analyzed during the current study are available from the corresponding author on reasonable request.¹² In each such case, compliance of data sharing with individual processes of patient consenting in participating centers will be reviewed.

Standard protocol approvals, registration, and patient consents

Protocols for the included clinical CeAD patient cohorts were approved by local authorities and ethics committees of all participating centers. Data collection and data analyses were conducted according to national rules of approval and informed consent of the included patients.

Results

Study population and baseline characteristics

Of the 2,526 patients with CeAD in the CADISP-Plus dataset, we included 2,148 patients with CeAD (85%) in whom data on functional outcome and presence or absence of DAO were available. Median age of the study population was 45 years (interquartile range [IQR] 38–52) and 43.6% of the population was women. DAO at first assessment was present in 728/2,148 patients (33.9%). In both groups, the majority of patients had ICAD (66.1% in patients with DAO and 63.5% in patients without DAO).

CIE at baseline were more frequent in patients with DAO than in patients without DAO (84.6% vs 58.5%, $p_{\text{unadjusted}} < 0.001$). Patients with DAO and ischemic stroke were also more severely affected than patients without DAO with ischemic stroke, as measured by the NIHSS (median NIHSS score [IQR] 4 [1–12] vs 1 [0–4], $p_{\text{unadjusted}} < 0.001$). Likewise, patients with DAO received acute recanalization therapies more frequently than did patients without DAO (16.5% vs 5.4%, $p_{\text{unadjusted}} < 0.001$). In turn, local signs (i.e., Horner syndrome, tinnitus, cervical pain) were significantly more common in patients without DAO (table 1). Vascular risk factors were equally common in both groups (table 1).

Outcome analyses

Primary and secondary analyses

Patients with DAO were less likely to have a favorable outcome when compared to patients without DAO (mRS 0–1 in 59.6% vs 80.1% of patients, $p_{\text{unadjusted}} < 0.001$, odds ratio [OR] [95% confidence interval (CI)] 0.36 [0.30–0.45]). In turn, the rate of CEI during follow-up time was higher in patients with DAO (4.5% vs 2.9%); however, this difference was not statistically significant ($p_{\text{unadjusted}} = 0.059$). In multivariable regression analysis including age, sex, and NIHSS score at baseline, DAO was independently associated with less favorable functional outcome (OR_{adjusted} [95% CI] 0.65 [0.50–0.84], $p_{\text{adjusted}} = 0.001$). This association did not change in secondary multivariable regression analyses including the aforementioned covariates as well as CEI, hemorrhage, and recurrent CeAD during follow-up (OR_{adjusted} [95% CI] 0.66 [0.50–0.88], 0.70 [0.52–0.94], $p_{\text{adjusted}} = 0.002$, tables 2 and 3).

Sensitivity analyses

We investigated the association of DAO and functional outcome separately for patients with ICAD and patients with VAD (excluding patients with multiple dissections; table 4). Favorable outcome was less frequent in patients with DAO with ICAD (patients with DAO 53.6% vs patients without DAO 80.3%, $p_{\text{unadjusted}} < 0.001$) or VAD (patients with DAO 68.8% vs patients without DAO 78.9%, $p_{\text{unadjusted}} < 0.001$). In multivariable regression analyses (including the same covariates integrated in the primary analyses), DAO was independently associated with less favorable outcome in

Table 1 Patient baseline characteristics and comparisons of patients with or without occlusion of the dissected artery

	All patients (n = 2,148)	Occlusion (n = 728)	No occlusion (n = 1,420)	p Value _{unadjusted}	OR _{crude} (95% CI)
Sex, female, n (%)	936 (43.6)	289 (39.7)	647 (45.6)	0.009	0.79 (0.66–0.94)
Age, y, median (IQR)	45 (38–52)	46 (39–52)	45 (38–52)	0.019	NA
Internal carotid artery dissection, n (%) ^a	1,382 (64.3)	481 (66.1)	901 (63.5)	0.23	1.12 (0.93–1.35)
Vertebral artery dissection, n (%) ^a	860 (40)	275 (37.8)	585 (41.2)	0.125	0.87 (0.72–1.04)
CIE at baseline, n (%)	1,446 (67.3)	616 (84.6)	830 (58.5)	<0.001	3.91 (3.12–4.91)
NIHSS score at admission, median (IQR)	2 (0–7)	4 (1–12)	1 (0–4)	<0.001	NA
Horner syndrome, n (%) ^b	553/1,364 (40.5)	147/474 (31)	406/890 (45.6)	<0.001	0.54 (0.42–0.68)
Tinnitus, n (%)	162/2,122 (7.6)	35/719 (4.9)	127/1,403 (9.1)	0.001	0.51 (0.35–0.76)
Cervical pain, n (%)	1,030/2,120 (48.6)	314/719 (43.7)	716/1,401 (51.1)	0.001	0.74 (0.62–0.89)
Headache, n (%)	1,430/2,121 (67.4)	470/719 (65.4)	960/1,402 (68.5)	0.149	0.87 (0.72–1.05)
Mechanical trigger event, n (%)	741/2,130 (34.8)	229/722 (31.7)	512/1,408 (36.4)	0.033	0.81 (0.67–0.98)
Migraine, n (%)	677/2,127 (31.8)	203/724 (28)	474/1,403 (33.8)	0.007	0.76 (0.63–0.93)
Hypertension, n (%)	69/2,128 (3.2)	200/723 (27.7)	351/1,402 (25)	0.19	1.15 (0.94–1.40)
Hypercholesterolemia, n (%)	603/1,997 (30.2)	220/684 (32.2)	383/1,313 (29.2)	0.167	1.15 (0.94–1.41)
Diabetes, n (%)	551/2,125 (25.9)	24/723 (3.3)	45/1,405 (3.2)	0.886	1.04 (0.63–1.72)
Acute recanalization therapy, n (%)	178/1,927 (9.2)	109/660 (16.5)	69/1,267 (5.4)	<0.001	3.44 (2.49–4.72)
Secondary prophylaxis, antiplatelets, n (%)	765/2,117 (36.1)	262/720 (36.4)	503/1,397 (36)	0.862	1.02 (0.84–1.23)
Secondary prophylaxis, anticoagulants, n (%)	1,255/2,117 (59.3)	439/720 (61)	816/1,397 (58.4)	0.256	1.11 (0.93–1.34)

Abbreviations: CI = confidence interval; CIE = cerebral ischemic event; IQR = interquartile range; NA = not applicable; NIHSS = NIH Stroke Scale; OR = odds ratio.

^a Numbers for internal carotid and vertebral artery dissection include patients presenting with multiple artery dissection.

^b In patients with internal carotid artery dissection. Data may not be available for all patients, thus total numbers of patients for each variable may vary.

patients with ICAD (OR_{adjusted} [95% CI] 0.53 [0.37–0.75], $p_{\text{adjusted}} = 0.001$). In patients with VAD, however, this association could not be confirmed (OR_{adjusted} [95% CI] 0.99 [0.65–1.50], $p_{\text{adjusted}} = 0.956$).

In prior research, Horner syndrome and tinnitus have been shown to predict favorable outcome in patients with CeAD and ICAD. Thus we included these variables in our multivariable regression model using favorable outcome (mRS 0–1) as outcome measure (table 5). In patients with ICAD, Horner syndrome was independently associated with a more favorable outcome (OR_{adjusted} [95% CI] 1.46 [1.01–2.10], $p_{\text{adjusted}} = 0.043$). A nonsignificant association in the same direction (statistically nonsignificant) was seen for presence of tinnitus at baseline (OR_{adjusted} [95% CI] 1.81 [0.84–3.88], $p = 0.13$). In this model (in patients with ICAD and including Horner syndrome and tinnitus as covariates), DAO remained independently associated with less favorable outcome.

We further performed univariate and multivariable (age, sex, DAO as covariates) regression analyses assessing the association of DAO and 3-month outcome (mRS 0–1) in patients with (1) no CIE, (2) TIA only, and (3) ischemic stroke only at

baseline. In all separate groups, DAO significantly reduced the likelihood of favorable outcome in both univariable and multivariable analyses (table 6). In patients without CIE at baseline, post hoc analyses triggered by the aforementioned findings revealed a significantly higher number of patients with CIE during follow-up in patients with DAO (8/111; 7.2%) than in patients without DAO (3/574; 0.52%) (OR_{crude} [95% CI] 14.8 [3.9–56.6], $p_{\text{crude}} < 0.001$).

As detailed in table 7, patients with DAO were more likely to have a major hemorrhage during follow-up than were patients without DAO. Triggered by these findings, we further explored the distribution of acute recanalization therapies and secondary prophylaxis (antiplatelet vs anticoagulation) in patients with major hemorrhage (extracranial or intracranial) during follow-up stratified to the presence of DAO (table e-1, doi:10.5061/dryad.q5b3621).

Discussion

Our analyses based on a large compilation of individual patient data derived from CeAD patient cohorts investigating the

Table 2 Predictors of functional outcome (i.e., modified Rankin Scale [mRS] 0–1)

	Univariate analyses (mRS 0–1)		Multivariable analyses (mRS 0–1)	
	<i>p</i> Value	OR (95% CI)	<i>p</i> Value	OR (95% CI)
Age	<0.001	0.98 (0.97–0.99)	0.001	0.98 (0.97–0.99)
Sex	0.077	1.19 (0.98–1.45)	0.502	0.91 (0.70–1.18)
NIHSS at admission	<0.001	0.82 (0.80–0.84)	<0.001	0.83 (0.81–0.85)
Dissected artery occlusion	<0.001	0.37 (0.30–0.45)	0.001	0.65 (0.50–0.84)

Abbreviations: CI = confidence interval; NIHSS = NIH Stroke Scale; OR = odds ratio.

impact of DAO on outcome in patients with CeAD revealed the following key findings. First, patients with DAO expectedly differed from patients without DAO, with a higher rate of cerebral ischemic events and a lower rate of local symptoms at baseline. Second, and as a novelty, DAO was an important and independent predictor of unfavorable functional outcome.

DAO is common in patients with CeAD. The frequency of DAO in our study population (i.e., 1/3) is in line with prior research.³

In our study population, patients with DAO differed from patients without DAO with regard to presenting symptoms. Most importantly and as to be expected, cerebral ischemia at baseline was more frequent in patients with DAO. Intraluminal growth of the mural hematoma in the dissected artery leads to hemodynamic impairment and can ultimately lead to an occlusion of the affected artery.^{15,16} Hemodynamic infarction or local thrombosis with later, secondary embolic infarction into distal arteries may consequently occur⁷ and can be expected at a higher frequency than in patients without DAO with CeAD as in the latter cerebral perfusion is at least partially ensured. Thus, stroke mechanisms in patients with CeAD with and without DAO may differ while infarction in

the latter is presumed to be due to primary embolism from the site of the dissection.^{7,17} Compensatory recruitment of collaterals or favorable baseline collateral status may prevent hemodynamic infarction in case of acute occlusion of cervical arteries. Although there are no reports specifically investigating collateral status in patients with CeAD, one might assume that due to acute rather than gradual, chronic cerebral hypoperfusion, such collaterals are poorly developed and thus lead to a high rate of cerebral ischemia in DAO. Indeed, in a small study investigating recanalization of the dissected artery, presence of collaterals was associated with a higher likelihood of nondisabling ischemic stroke rather than severe disabling ischemic stroke.¹⁸ Likewise, in VAD, the non-affected contralateral artery might compensate for occlusion in the affected artery, an effect supported by our analyses in which worse outcome in patients with DAO was almost exclusively seen in ICAD rather than VAD. In the present study, patients with DAO with cerebral ischemia at baseline were also more severely affected as measured by a higher median NIHSS score at baseline. This is supported by the aforementioned differences in stroke pathophysiology in patients with vs without DAO with CeAD and data from prior research.¹⁹ One prior study reported significantly larger cortical and subcortical infarcts with global involvement of the middle

Table 3 Multivariable regression analyses on favorable functional outcome including covariates

	Univariate analyses (mRS 0–1)		Multivariable analyses (mRS 0–1)	
	<i>p</i> Value	OR (95% CI)	<i>p</i> Value	OR (95% CI)
Age	See table 3		<0.001	0.97 (0.96–0.99)
Sex			0.209	0.83 (0.62–1.11)
NIHSS at admission			<0.001	0.80 (0.78–0.83)
Dissected artery occlusion			0.002	0.66 (0.50–0.88)
CIE during follow-up period	0.007	0.52 (0.32–0.84)	0.002	0.34 (0.17–0.67)
Recurrent CeAD during follow-up period	0.645	1.19 (0.56–2.53)	0.908	1.07 (0.32–3.56)
Major hemorrhage (intracranial or extracranial) during follow-up period	0.028	0.29 (0.1–0.88)	0.41	0.51 (0.10–2.55)

Abbreviations: CI = confidence interval; CeAD = cervical artery dissection; CIE = cerebral ischemic events; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio.

Table 4 Sensitivity analyses: Outcome analyses on 3-month outcome in all patients with internal carotid artery dissection (ICAD) and vertebral artery dissection (VAD)

ICAD (total = 1,286 patients ^a)	ICAD with occlusion (n = 453)		ICAD without occlusion (n = 833)		p Value	OR (95% CI)
Favorable outcome, n (%)	243 (53.6)		728 (80.3)		<0.001	0.29 (0.22–0.37)
Predictors of outcome, ICAD	Univariate analyses (mRS 0–1)		Multivariable analyses (mRS 0–1)		p Value	OR (95% CI)
	p Value	OR (95% CI)	p Value	OR (95% CI)		
Age	0.966	1.00 (0.99–1.01)	0.443	0.99 (0.98–1.01)		
Sex	0.215	1.17 (0.91–1.50)	0.593	0.91 (0.64–1.30)		
NIHSS at admission	<0.001	0.82 (0.79–0.84)	<0.001	0.83 (0.80–0.85)		
Dissected artery occlusion	<0.001	0.28 (0.22–0.37)	0.001	0.53 (0.37–0.75)		
VAD (total = 764 patients ^a)	VAD with occlusion (n = 247)		VAD without occlusion (n = 517)		p Value	OR (95% CI)
Favorable outcome, n (%)	170 (68.8)		408 (78.9)		0.002	0.59 (0.42–0.83)
Predictors of outcome, VAD	Univariate analyses (mRS 0–1)		Multivariable analyses (mRS 0–1)		p Value	OR (95% CI)
	p Value	OR (95% CI)	p Value	OR (95% CI)		
Age	<0.001	0.96 (0.94–0.97)	<0.001	0.96 (0.95–0.98)		
Sex	0.27	1.21 (0.87–1.68)	0.787	0.95 (0.63–1.42)		
NIHSS at admission	<0.001	0.83 (0.79–0.88)	<0.001	0.83 (0.79–0.88)		
Dissected artery occlusion	0.003	0.59 (0.42–0.83)	0.956	0.99 (0.65–1.50)		

Abbreviations: CI = confidence interval; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio.

^a All analyses performed excluding patients with multiple dissections at baseline.

cerebral artery territory in patients with DAO with CeAD compared to patients with stroke with atherothrombotic occlusion of the cervical ICA.⁷ Another study comparing patients with stroke with nondissectional carotid stenosis to those with carotid occlusion also showed significantly more severe stroke in patients with artery occlusion.²⁰

Contrary to the frequency of cerebral ischemia in patients with DAO in our population, local signs of CeAD were less frequent in patients with DAO when compared to patients without DAO. Horner syndrome in ICAD is assumed to

result from local compression of the sympathetic plexus surrounding the affected artery.²¹ In VAD, Horner syndrome is caused by brainstem ischemia.⁴ Thus, with DAO being caused by intraluminal expansion of the mural hematoma rather than eccentric expansion, the differences in frequency of Horner syndrome in both groups can be explained in ICAD. While we have not investigated differential features of patients with DAO with ICAD and VAD, in a prior study, also including patients from the CADISP-1 cohort, DAO in VAD was more common in patients with Horner syndrome, which is supported by the different pathophysiology of Horner syndrome

Table 5 Sensitivity analyses: Multivariable regression outcome analyses in patients with internal carotid artery dissection (ICAD) (n = 1,382) including known predictors of favorable outcome

	Univariate analysis (mRS 0–1)		Multivariable analysis (mRS 0–1)	
	p Value	OR (95% CI)	p Value	OR (95% CI)
Age	0.949	1.00 (0.99–1.01)	0.343	0.99 (0.98–1.01)
Sex	0.249	1.15 (0.91–1.47)	0.556	0.90 (0.63–1.28)
NIHSS at admission	<0.001	0.82 (0.79–0.84)	<0.001	0.83 (0.81–0.85)
Dissected artery occlusion	<0.001	0.29 (0.23–0.37)	<0.001	0.54 (0.38–0.75)
Horner syndrome at baseline	<0.001	2.92 (2.23–3.82)	0.043	1.46 (1.01–2.10)
Tinnitus at baseline	<0.001	4.11 (2.29–7.37)	0.13	1.81 (0.84–3.88)

Abbreviations: CI = confidence interval; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio.

Table 6 Sensitivity analyses: Multivariable regression outcome (modified Rankin Scale [mRS] 0–1) analyses in patients with no cerebral ischemia at baseline, TIA at baseline, and ischemic stroke at baseline

Group	Outcome predictor	Univariate analysis (mRS 0–1)		Multivariable analysis (mRS 0–1) ^a	
		p Value	OR (95% CI)	p Value	OR (95% CI)
No CIE at baseline	Occlusion of dissected artery	0.015	0.52 (0.30–0.88)	0.023	0.52 (0.30–0.91)
TIA	Occlusion of dissected artery	<0.001	0.33 (0.20–0.54)	<0.001	0.34 (0.21–0.56)
Ischemic stroke	Occlusion of dissected artery	<0.001	0.53 (0.41–0.69)	<0.001	0.55 (0.42–0.71)

Abbreviations: CI = confidence interval; CIE = cerebral ischemic events; OR = odds ratio.

^a Adjusted for age and sex.

in ICAD and VAD.⁵ Pulsatile tinnitus in CeAD is assumed to occur by local flow acceleration and turbulence at the site of dissection and thus cannot be expected in DAO.^{6,22,23} In our sensitivity analyses, we included presence of Horner syndrome and tinnitus at baseline in our multivariable regression model (in patients with ICAD) and confirmed the predictive value of a more favorable outcome in patients with CeAD with these local signs present at baseline.

Most importantly, this study demonstrates that occlusion of the dissected artery independently predicts a less favorable functional outcome in patients with CeAD. In multivariable analyses including known predictors of less favorable outcome in patients with stroke (age, sex, NIHSS), DAO retains its strong, statistically significant predictive value. As shown in a prior study, DAO may be a risk factor for delayed ischemic events in patients with CeAD.⁸ Indeed, we identified more ischemic strokes or TIAs during follow-up in patients with DAO at baseline. Likewise, major hemorrhage was more common in patients with DAO during follow-up. We included these covariates as well as occurrence of recurrent CeAD in our multivariable sensitivity analyses, yet DAO remained a strong independent predictor of less favorable functional outcome. Interestingly, in our multivariable

sensitivity analyses, we confirmed these results in separate subgroups of patients without (1) any cerebral ischemia at baseline, (2) TIA at baseline, and (3) stroke at baseline. In particular, in those patients without ischemia or TIA at baseline, this is a remarkable finding, suggesting mechanisms of chronic mild cerebral hypoperfusion leading to a less favorable outcome in patients with DAO with CeAD. Our separate analyses of ICAD and VAD might support this theory, as the effect of DAO on outcome seemed to be almost exclusively driven by patients with ICAD in whom crossflow or collateral perfusion might be less effective than the supporting perfusion by a contralateral, nonaffected VAD in the posterior circulation. On the other hand, in post hoc analysis we also identified significantly more CIE during follow-up in this subgroup of patients with DAO (those without CIE at baseline) compared to patients without DAO. Although this might per se be explanatory for a worse functional outcome, numbers of events in these subgroups were very low and thus these findings have to be interpreted very cautiously.

An important strength of our study is the sample size, which minimizes risks of chance findings and allowed us to adjust for potential confounders of outcome in multivariable analyses.

Table 7 Primary and secondary outcomes in patients with or without dissected artery occlusion

	All patients (n = 2,148)	Occlusion (n = 728)	No occlusion (n = 1,420)	p Value _{unadjusted}	OR (95% CI) _{unadjusted}
Primary outcome					
Favorable outcome (i.e., mRS 0–1)	1,572 (73.2)	434 (59.6)	1,138 (80.1)	<0.001	0.36 (0.30–0.45)
Secondary outcomes^a					
CIE	72/2098 (3.4)	32/715 (4.5)	40/1,383 (2.9)	0.059	1.57 (0.98–2.53)
Recurrent CeAD	39/2095 (1.9)	14/713 (2)	25/1,382 (1.8)	0.804	1.09 (0.56–2.10)
Major hemorrhage (intracranial or extracranial)	13/1957 (0.7)	8/655 (1.2)	5/1,292 (0.4)	0.038	3.13 (1.02–9.62)
Death	28 (1.3)	15/728 (2.1)	13/1,420 (0.9)	0.027	2.28 (1.08–4.81)

Abbreviations: CeAD = cervical artery dissection; CI = confidence interval; CIE = cerebral ischemic events; mRS = modified Rankin Scale; OR = odds ratio. Data may not be available for all patients, thus total numbers of patients for each variable may vary. Values are n (%).

^a During follow-up time.

Although secondary analyses have to be interpreted cautiously, we were thus able to confirm the main effect of the prognostic importance of DAO in patients with CeAD also in predefined subgroups of patients and thus present a vigorous and comprehensive analysis of this outcome predictor.

We are aware of the following limitations of our study: (1) our analyses are based on data from large CeAD patient cohorts recruited at departments of neurology only, and that are nonrandomized and not monitored; (2) we did not exclude patients with pre-CeAD mRS >1 from the analysis as these data were not collected, but considering that only 26% of patients had a post-CeAD mRS >1, this is unlikely to have jeopardized our key findings; (3) the rate of acute recanalization therapy was lower than would be expected in the current environment of acute recanalization therapies, which might have caused bias towards worse outcome in patients with DAO, who probably would have benefited in particular from EVT; and (4) data on (1) presence vs absence of an occlusion of intracranial arteries downstream of the dissected arteries as well as (2) recanalization, either spontaneously or after acute recanalization therapy, were not available, although we were able to include follow-up data with a high completeness of the collected data.

Knowledge of the course of disease, the extent of expectable functional recovery, as well as risks of recurrences and complications and determining factors of these are crucial for informed, safe, and individualized treatment of patients with CeAD in clinical routine. Our findings emphasize the importance of vascular findings in patients with CeAD. Although there is not yet supporting evidence for superiority of endovascular treatment in patients with CeAD,²⁴ our findings might support a more rigorous approach in the implementation of EVT in patients with CeAD, in particular those with DAO.

DAO independently predicts unfavorable outcome in patients with CeAD, which may support clinicians in individually tailored decision-making on acute treatment and monitoring. Further research is warranted and should particularly focus on vessel patency status, the effect of collateral status on outcome and treatment effects, as well as best acute recanalization therapies and secondary prophylaxis, in particular in patients with CeAD with DAO.

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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B15.

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