Prognosis of carotid dissecting aneurysms

Results from CADISS and a systematic review

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ABSTRACT

Objective: To determine the natural history of dissecting aneurysm (DA) and whether DA is associated with an increased recurrent stroke risk and whether type of antithrombotic drugs (antiplatelets vs anticoagulants) modifies the persistence or development of DA.

Methods: We included 264 patients with extracranial cervical artery dissection (CAD) from the Cervical Artery Dissection in Stroke Study (CADISS), a multicenter prospective study that compared antiplatelet with anticoagulation therapy. Logistic regression was used to estimate age- and sex-adjusted odds ratios. We conducted a systematic review of published studies assessing the natural history of DA and stroke risk in patients with non-surgically-treated extracranial CAD with DA.

Results: In CADISS, DA was present in 24 of 264 patients at baseline. In 36 of 248 patients with follow-up neuroimaging at 3 months, 12 of the 24 baseline DAs persisted, and 24 new DA had developed. There was no association between treatment allocation (antiplatelets vs anticoagulants) and whether DA at baseline persisted at follow-up or whether new DA developed. During 12 months of follow-up, stroke occurred in 1 of 48 patients with DA and in 7 of 216 patients without DA (age- and sex-adjusted odds ratio 0.84; 95% confidence interval 0.10–7.31; p = 0.88). Published studies, mainly retrospective, showed a similarly low risk of stroke and no evidence of an increased stroke rate in patients with DA.

Conclusions: The results of CADISS provide evidence suggesting that DAs may have benign prognosis and therefore medical treatment should be considered. *Neurology*® 2017;88:646–652

GLOSSARY

CAD = cervical artery dissection; **CADISS** = Cervical Artery Dissection in Stroke Study; **CI** = confidence interval; **CTA** = CT angiography; **DA** = dissecting aneurysm; **ICA** = internal carotid artery; **MRA** = magnetic resonance angiography; **NR** = nonrandomized; **OR** = odds ratio; **VA** = vertebral artery.

Cervical artery dissection (CAD) is an important cause of stroke in younger adults.[1] A common angiographic consequence is dissecting aneurysm (DA), also called false or pseudoaneurysm, occurring in 13%–49% of patients with CAD.[2–12] It has been suggested that DAs indicate increased stroke risk, either as a source of embolization or via expansion and compressive symptoms. This has led some specialists to treat DA; in a recent study, 20% were obliterated with stenting and coiling.[12] Other authorities suggest the risk of stroke in CAD is low and no treatment is required. Small studies report low stroke risk,[4–7,10] but these are retrospective with incomplete case ascertainment. Data from prospective studies with predefined clinical and imaging follow-up protocols are limited.[11]

The Cervical Artery Dissection in Stroke Study (CADISS) was a randomized controlled trial comparing antiplatelet with anticoagulant therapy in CAD.[13,14] In addition, patients who did not meet the inclusion criteria or where the patient or doctor were not prepared to randomize were recruited to the nonrandomized arm.[15] Angiographic imaging was reviewed at baseline and

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Table 1 Number (%) of patients with dissecting aneurysm (DA) at baseline and 3 months in the Cervical Artery Dissection in Stroke Study

	In 264 patients with imaging at baseline			In 248 patients with follow-up imaging at 3 months					
	Baseline			Baseline			3 months		
DA	All	ICA	VA	All	ICA	VA	All	ICA	VA
Yes	24 (9.1)	13 (10.6)	11 (7.8)	24 (9.7)	13 (11.3)	11 (8.3)	36 (14.5)	21 (18.3)	15 (11.3)
No	240 (90.9)	110 (89.4)	130 (92.2)	224 (90.3)	102 (88.7)	122 (91.7)	212 (85.5)	94 (81.7)	118 (88.7)

Abbreviations: ICA = internal carotid artery; VA = vertebral artery.

repeated in the majority of participants at 3 months. This provides robust data from a prospective study on the prevalence and outcome of DA.

We determined the incidence and risk factors for DA in CADISS, their natural history on angiographic imaging, and whether they were associated with an increased recurrent stroke risk. We also examined whether type of antithrombotic drugs (antiplatelets vs anticoagulants) was associated with the persistence or development of DA. In addition, we performed a systematic review of published studies assessing the natural history of DA and stroke risk in patients with non-surgically-treated extracranial CAD with DA.

METHODS

Participants. CADISS was a multicenter prospective study comparing anticoagulation with antiplatelet therapy in patients with CAD. Full details with follow-up to the 3-month primary endpoint have been published previously.[13,14] A total of 250 patients were randomized 1:1 via an automated 24-hour telephone randomization service to a treatment regimen of antiplatelet agents or anticoagulants for 3 months in an open design with blinded evaluation of endpoints. Inclusion criteria were extracranial carotid or vertebral artery dissection with symptom onset within the last 7 days, in combination with imaging evidence of definite or probable dissection. If the patient had had a stroke or TIA within the last 7 days he or she was eligible even if this was preceded by local symptoms with onset more than 7 days previously. Imaging evidence of definite or probable dissection had to be on MRI/magnetic resonance angiography (MRA), CT angiography (CTA), or intra-arterial angiography. Exclusion criteria were intracranial cerebral artery dissection; contraindications to antiplatelet agents or anticoagulation therapy, including active peptic ulceration or bleeding peptic ulcer within 1 year; patient refusal to consent; patient already taking antiplatelet agents or anticoagulants for other reasons; and pregnancy. Patients not eligible for inclusion in the randomized arm, or where the doctor or patient did not accept randomization, were recruited to the nonrandomized arm (CADISS-NR) if they were within 31 days of symptom onset.[15] Patients in CADISS-NR underwent the same imaging and clinical follow-up protocol.

Standard protocol approvals, registrations, and patient consents. The local ethics committee approved the study, and all patients provided written consent.

Data collection and outcome assessment. Patients were seen in person for follow-up at 3 months postrandomization. Data on outcome and occurrence of recurrent stroke and TIA were recorded. Repeat imaging with MRA or CTA was performed

Table 2 Characteristics of patients with and without dissecting aneurysm (DA) at baseline or 3 months in the Cervical Artery Dissection in Stroke Study

	DA at baseline or 3 months			No DA at any time point			
Characteristic[a]	All (48)	ICA (27)	VA (21)	All (216)	ICA (96)	VA (120)	*p* Value[b]
Age, y	44.7 (10.3)	47.6 (8.8)	41.1 (11.1)	47.6 (11.9)	46.0 (10.4)	48.8 (12.9)	0.13
Female	15 (31.3)	8 (29.6)	7 (33.3)	77 (35.6)	37 (38.5)	40 (33.3)	0.56
Treated hypertension	7 (14.6)	4 (14.8)	3 (14.3)	47 (21.8)	16 (16.7)	31 (25)	0.27
Diabetes mellitus	1 (2.1)	1 (3.7)	0 (0)	9 (4.2)	3 (3.1)	6 (5.0)	0.49
Current smoker	7 (14.6)	4 (14.8)	3 (14.3)	54 (25.0)	26 (27.1)	28 (23.3)	0.12
Statin therapy	6 (12.5)	5 (18.5)	1 (4.8)	48 (22.2)	23 (24.0)	25 (20.8)	0.13
History of recent trauma (<30 d)	15 (31.3)	8 (29.6)	7 (33.3)	50 (23.3)	25 (26.0)	25 (20.8)	0.25
Migraine	9 (18.8)	6 (22.2)	3 (14.3)	40 (18.6)	21 (21.9)	19 (15.8)	0.99
Thrombolysis for stroke	5 (10.4)	4 (14.8)	1 (4.8)	17 (7.9)	10 (10.4)	7 (5.8)	0.57

Abbreviations: ICA = internal carotid artery; VA = vertebral artery.
[a] Data are presented as n (%), except for age, which is presented as mean (SD).
[b] *p* Value for difference in baseline characteristic for all patients without DA vs all patients with DA at any point.

Table 3 Associations of antiplatelet and anticoagulant therapy with persistence of dissecting aneurysm (DA) and development of new DA at 3 months follow-up in the Cervical Artery Dissection in Stroke Study

Outcome	Antiplatelet therapy (n = 139)	Anticoagulant therapy (n = 109)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	p Value[a]
Persistent DA	8/14 (57)[b]	4/10 (40)[b]	0.50 (0.10–2.60)	0.57 (0.09–3.51)	0.54
New DA	12/125 (10)[b,c]	12/99 (12)[b,c]	1.33 (0.66–2.70)	1.34 (0.66–2.71)	0.42

Abbreviations: CI = confidence interval; OR = odds ratio.
[a] Adjusted for age and sex.
[b] Number of patients with persistent DA or new DA/total number of patients in the group (% with persistent DA or new DA).
[c] Excluding patients with DA at baseline.

whenever possible at 3 months to assess vessel recanalization. All radiology images at baseline and 3 months were reviewed by a consultant neuroradiologist in the coordinating center who was blinded to treatment allocation. Telephone follow-up was performed at 6 and 12 months and in cases of possible stroke original records and scans were reviewed. All stroke cases were adjudicated by a committee blinded to patient treatment and the results of angiographic imaging.

Participants included in the present analysis. On central radiology review, there were confirmatory features of a dissection in 197 of 250 patients, and in 1 additional patient; although the patient was recruited within 7 days, due to a technical problem with the randomization process, randomization itself occurred on day 9. Therefore 197 patients were included in the analysis, in addition to 67 patients with centrally confirmed imaging appearances of dissection in the NR arm. These 264 patients were included in the present analysis. Follow-up was complete at 1 year in all 264 patients.

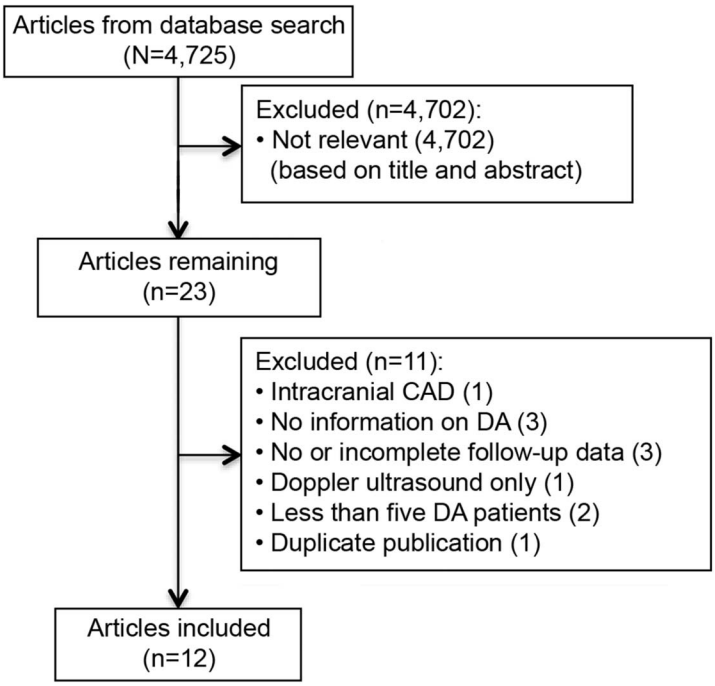
Statistical analysis. Characteristics of patients with and without DA were compared using t and χ^2 tests. Logistic regression was used to estimate age- and sex-adjusted odds ratios (ORs) with 95% confidence intervals (CIs). The statistical analyses were performed using Stata version 14.1 (StataCorp, College Station, TX). All tests were 2-sided and p values < 0.05 were considered statistically significant.

Systematic review. Relevant studies were identified by searches of PubMed (including MEDLINE) from inception to October 15, 2016, using the search terms carotid artery, vertebral artery, or extracranial artery combined with pseudoaneurysms, dissecting aneurysms, or false aneurysms. No language or other restrictions were imposed. The reference lists of retrieved publications were reviewed to search for additional studies. Two authors (S.C.L., A.K.) performed the literature search. Inclusion criteria were (1) prospective or retrospective longitudinal study; and (2) reported results on anatomical or clinical outcome of aneurysmal forms of extracranial CAD in medically treated patients. Exclusion criteria were intracranial CAD, invasive treatment of patients, fewer than 5 patients with extracranial CAD with DA, case-report, case-control, or cross-sectional study, nonhuman study, and other nonrelevant reports not meeting the inclusion criteria.

Data were extracted independently by 2 authors (S.C.L., H.S.M.), and any disagreement was resolved by consensus. The following information was extracted: last name of the first author, publication year, study design (prospective or retrospective), number of patients, mean age of patients, mean follow-up time, imaging modality for follow-up, time between symptom and angiography, number of dissecting aneurysms and affected vessel, anatomical findings from follow-up imaging, and clinical outcome events (any fatal or nonfatal stroke).

Data on the presence and anatomical outcome of DA were only taken from studies that performed angiographic imaging at baseline and follow-up with CTA, MRA, or digital subtraction angiography. Studies with Doppler ultrasound alone follow-up were not included as this has a low sensitivity for detecting DA.

Figure Flowchart of study selection



CAD = cervical artery dissection; DA = dissecting aneurysm.

RESULTS

CADISS. On central imaging review, a DA was present in 24 (9.1%) of the 264 patients at baseline (table 1). Follow-up MRA or CTA at 3 months was present and of adequate quality for central radiologic review for 248 of the 264 patients. Analysis of these 248 patients showed that DA was present at baseline in 24 (9.7%). At a median follow-up of 3.2 months (interquartile range 3.0–3.5 months), 12 (6 internal carotid artery [ICA] and 6 vertebral artery [VA]) of the 24 baseline DAs persisted whereas 12 DAs (7 ICA and 5 VA) had resolved. In addition, 24 new DAs (14 ICA and 10 VA) had developed. Patients with and without DA did not differ significantly with regard to age, sex, vascular

Table 4 Previous studies of anatomic outcome of dissecting aneurysms (DAs) due to cervical artery dissection in medically treated patients

Reference	Study design	Imaging modality for DA diagnosis	Mean time between repeated imaging, mo	Patient population	Dissecting aneurysms			Angiographic findings for ICA[a]				Angiographic findings for VA[b]			
					Total DA	ICA	VA	Unchanged	Resolved	Decreased	Enlarged	Unchanged	Resolved	Decreased	Enlarged
16	Retrospective[b]	CA/DSA	64	Spontaneous	18	20	0	6 (33)	4 (22)	8 (45)	0				
			40	Traumatic	12	14[c]	0	5 (63)	1 (12)	2 (25)	0	—	—	—	—
17	Retrospective	CA/CTA	24	Symptomatic	8	8	0	4 (50)	4 (50)	0	0	—	—	—	—
4	Retrospective	CA/MRA	37	Symptomatic <30 days	20	20	0	13 (65)	1 (5)	6 (30)	0	—	—	—	—
5	Retrospective	MRA	41	Symptomatic mostly <30 days	26	26	0	20 (77)	2 (8)	4 (15)	0	—	—	—	—
6	Recall of prospectively recruited cohort	MRA	42	Symptomatic arteries	28	22	6	10 (46)	8 (36)	4 (18)	0	1 (17)	5 (83)	0	0
				Asymptomatic arteries	12	10	2	9 (90)	0	1 (10)	0	0	2 (100)	0	0
7	Retrospective	DSA	4	Symptomatic (<28 days in >90%)[d]	11	11	0	8 (73)	1 (9)	2 (18)	0	—	—	—	—
18	Prospective and retrospective components	CTA/DSA	22	Screening of patients presenting with blunt trauma	26	25	1	1 (4)	10 (38)	10 (38)	5 (19)	—	—	—	—
19	Retrospective	CTA/MRA	Uncertain	Asymptomatic	52	0	52	—	—	—	—	50 (96)	5	1 (2)	1 (2)
				Pain only	56	0	56	—	—	—	—	38 (68)	0	15 (27)	3 (5)
				Mass effect	5	0	5	—	—	—	—	3 (60)	—	1 (20)	1 (20)
12	Retrospective	CTA/MRA	Uncertain	Uncertain	108[e]	NA	NA	60 (56)[f]	33 (30)[f]	0	15 (14)[f]	—	—	—	—
CADISS	Prospective	CTA/MRA	3	Symptomatic	24	13	11	6 (46)	7 (54)	0	0	6 (55)	5 (45)	0	0

Abbreviations: CA = conventional angiography; CTA = CT angiography; DSA = digital subtraction angiography; ICA = internal carotid artery; MRA = magnetic resonance angiography; NA = not available; VA = vertebral artery.

[a] Data are reported as number (%) of dissecting aneurysms that were unchanged or had resolved, decreased, or enlarged during follow-up.

[b] This study included patients from Mokri et al.[2] Because of overlapping case series only the most recent study by Mokri,[16] which included more patients, was included.

[c] Four DAs were eliminated by resection.

[d] One patient who had artery ligated was omitted from analysis.

[e] Including 18.3% intracranial dissecting aneurysms and 20.8% of patients received an intervention other than medical treatment.

[f] ICA and VA DAs combined.

Table 5 Studies of clinical outcome of dissecting aneurysm (DA) due to cervical artery dissection (CAD) in medically treated patients

Reference	Study design	Mean age, y	Time since symptom onset	Mean follow-up, mo	No. of CAD patients			No. of stroke cases during follow-up in CAD patients	
					Total[a]	ICA	VA	With DA	Without DA
4	Retrospective	47	<30 days	36.9	16	16	0	0/16	NA
5	Retrospective	52	<30 days and >30 days in 79% and 21% of patients, respectively	41	20	20	0	0/20	NA
6	Recall of prospectively recruited cohort (80% response rate)	44	Mean 11.6 days	41.6	35	35	0	0/35	NA
7	Retrospective	45	Mean 7.2 days	4	11/80	NA	NA	0/11	0/80
10	Retrospective	47	35/38 symptomatic; median 11 days and 9 months in 55% and 45% of patients, respectively	78	37	NA	NA	2/37[b]	NA
11	Prospective	42	29/33 symptomatic; 8 days	37	6/27	0	40	0/6	0/27
18	Prospective and retrospective components	32	Screening of patients presenting with major blunt trauma	15.8	13	12	1	0/13[c]	NA
19	Uncertain	55	Nonstroke; 52 asymptomatic, 56 pain, 5 mass effect	34.8	113	0	113	1/113[d]	NA
12	Retrospective	48	NA	29.3	89[e]	NA	NA	0/89	NA
CADISS	Prospective	47	<7 days	12	48/216	27/96	21/120	1/48	7/216

Abbreviations: CADISS = Cervical Artery Dissection in Stroke Study; ICA = internal carotid artery; NA = not available; VA = vertebral artery.
[a] Number of patients with CAD with/without DA.
[b] One patient who died of stroke at 14 days from initial stroke due to acute CAD was excluded.
[c] One patient noted to have asymptomatic bilateral anterior cerebral artery infarct at 2 weeks on MRI.
[d] Two additional patients developed symptoms due to mass effect.
[e] ICA and VA DA patients combined. Only patients not undergoing neurobiological or surgical intervention included.

risk factors, history of recent trauma, or use of IV thrombolysis (table 2). Treatment allocation (antiplatelets vs anticoagulants) did not modify whether DA at baseline persisted at the 3-month follow-up or whether new DA developed (table 3).

Follow-up data to the final follow-up of 12 months were obtained in all patients. Eight strokes (all ipsilateral) occurred during follow-up in the 264 patients. One of the events occurred in the 48 patients with DA at baseline or 3 months, and 7 occurred in the 216 patients without DA (age- and sex-adjusted OR 0.84; 95% CI 0.10–7.31, $p = 0.88$). There were too few events to determine whether antiplatelets or anticoagulants were more effective at preventing recurrent stroke in patients with DA: no stroke in 26 DA patients treated with antiplatelets and 1 stroke in 22 DA patients treated with anticoagulants.

Systematic review. The literature search identified 4,725 articles, of which 12 studies met the inclusion criteria (figure). Among the included studies, 9 provided data on anatomical outcome[4–7,12,16–19] and 9 provided data on clinical outcome[4–7,10–12,18,19] in patients with CAD with DA.

The definition used to define complete and partial resolution differed between studies but the results showed a very low rate of DA expansion with no cases of expansion in 8 of the 9 studies (table 4). The studies confirmed that many DAs resolved completely on follow-up imaging. The resolution rate appeared to be higher in patients initially imaged shortly after presentation and was lower in asymptomatic DAs, suggesting that if DAs are to resolve they tend to do so shortly after formation.

Seven studies provided outcome data in patients with CAD with DA but had no comparison group without DA[4–6,10,12,18,19]; combined, these studies included 323 patients with DAs, of whom 3 had a stroke (1 fatal and 1 capsular stroke in 1 study[10] and 1 nonfatal ischemic stroke in another study[19]) during follow-up (table 5). Only 2 studies compared clinical outcome in patients with CAD and without DA[7,11]; no strokes occurred in either group (table 5).

DISCUSSION In the prospective CADISS study, our data demonstrate that DA is a relatively common sequel to extracranial vessel dissection, has a benign prognosis, and the presence of a DA does not indicate that an individual with dissection is at higher risk of recurrent stroke. Our data further suggest that DA is a relatively dynamic process with a significant proportion of aneurysms either healing or developing over the initial 3 months following clinical diagnosis of vessel dissection. There was no difference in the

persistence of DA or development of new DA for antiplatelet vs anticoagulant therapy.

CADISS provides some of the most robust evidence on the prognosis of DA. Its prospective design and complete outcome ascertainment during follow-up makes it much less susceptible to bias than previous retrospective studies. During the 1-year follow-up, there were few recurrent strokes, and stroke risk in patients who had a DA on either initial imaging or 3-month imaging was no higher than those without DA. CADISS also provides data on the anatomical outcome of DA. The results showed that approximately half of all DA resolved entirely within the first 3 months, but that additional aneurysms appeared after the initial angiographic imaging.

The results of both the follow-up angiographic imaging and clinical follow-up in CADISS were broadly in agreement with those from our systematic review. This also showed a very low risk of recurrent strokes in patients with DA. However, most previous studies had significant limitations, including retrospective design and the potential for ascertainment bias and variable inclusion criteria. In addition, in some studies a proportion of patients had interventions other than medical therapy, for example coiling or surgical intervention.[12]

Despite their benign prognosis, a significant number of patients with DA are treated with interventions, the most common being coiling, which has an associated risk of stroke. Our data suggest that such interventions may not be warranted and medical treatment alone is sufficient, and indeed is likely to be safer. In CADISS, all patients were on either antiplatelet drugs or anticoagulants, and in the systematic review most patients were on antithrombotic medication. It is therefore impossible to determine from the available data whether patients with DA need long-term antithrombotic medication. There are occasional cases of DA where expansion occurs, resulting in compressive symptoms. There were no such cases in CADISS, and such complications appeared to be very rare, but in these exceptional cases intervention may be required.[12]

The results of CADISS provide robust evidence that DAs may have a benign prognosis and therefore medical treatment should be considered. This finding is consistent with those from a systematic review of previous largely retrospective observational studies.

AUTHOR CONTRIBUTIONS

Susanna Larsson performed the literature search, assessed the eligibility and extracted the data of identified studies, analyzed and interpreted the data, and drafted the manuscript. Alice King conducted the literature search, contributed to interpretation of the data, and revised the article critically for important intellectual content. Jeremy Madigan, Christopher Levi, and John Norris were involved in interpretation of the data and revised the article critically for important intellectual content. Hugh Markus conceived and designed the study, assessed the eligibility and extracted the data of identified studies, interpreted the data, and drafted the manuscript. The corresponding author attests that the authors had access to all the study data, takes responsibility for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication. All authors gave final approval of the version to be published. The corresponding author affirms that he has listed everyone who contributed substantially to the work.

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DISCLOSURE

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