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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) modify the persistence or development of DA.

Methods: We included 264 extracranial cervical artery dissection (CAD) patients from the Cervical Artery Dissection in Stroke Study (CADISS), a multicentre 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 non-surgically treated extracranial CAD patients 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 one of 48 patients with DA and in seven 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.

Keywords: aneurysms; cervical artery dissection; stroke

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 pseudo-aneurysm, occurring in 13-49% of CAD patients.[2-12] It has been suggested 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 randomised 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 randomise were recruited to the non-randomised arm.[15] Angiographic imaging was reviewed at baseline and 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 non-surgically treated extracranial CAD patients with DA.

METHODS

Participants. CADISS was a multicentre prospective study comparing anticoagulation with antiplatelet therapy in CAD patients. Full details with follow-up to the three month primary

endpoint have been published previously.[13, 14] 250 patients were randomised 1:1 via an automated 24 h 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 suffered stroke or transient ischaemic attack (TIA) within the last 7 days they were 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 MR imaging (MRI)/MR angiography (MRA), computed tomography 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; patients already taking antiplatelet agents or anticoagulants for other reasons; and pregnancy. Patients not eligible for inclusion in the randomised arm, or where the doctor or patient did not accept randomisation, were recruited to the nonrandomised 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 post-randomisation. Data on outcome and occurrence of recurrent stroke and TIA were recorded. Repeat imaging with MRA or CTA was performed whenever possible at 3 months to assess vessel recanalisation. All radiology images at baseline and 3 months were

reviewed by a consultant neuroradiologist in the coordinating centre 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 one additional patient, although the patient was recruited within 7 days, due to a technical problem with the randomisation process, randomisation 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 non-randomised 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 with 95% confidence intervals. The statistical analyses were performed using Stata version 14.1 (StataCorp, College Station, TX). All tests were two-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 13 October 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 (SCL, AK) performed the literature search. Inclusion criteria were: 1) prospective or

retrospective longitudinal study; 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, less than five extracranial CAD patients with DA, case-report, case-control or cross-sectional study, non-human study, and other non-relevant reports not meeting the inclusion criteria.

Data were extracted independently by two authors (SCL, HSM), 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 was only taken from studies that performed angiographic imaging at baseline and follow-up with CTA, MRA or DSA. Studies with Doppler ultrasound alone follow-up were not included as this has a low sensitivity for detecting DA.

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 radiological 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 (IQR 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, gender, vascular risk factors, history of recent trauma, or use

of intravenous thrombolysis (table 2). Treatment allocation (antiplatelets vs anticoagulants) did not modify whether DA at baseline persisted at the 3 months follow-up or whether new DA developed (table 3).

Follow-up data to the final follow-up of 12 months were obtained in all cases. 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 seven occurred in the 216 patients without DA (age- and sex-adjusted odds ratio, 0.84; 95% confidence interval, 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 29 patients with DA treated with antiplatelets, versus 1 stroke in 22 patients with DA treated with anticoagulants.

Systematic review. The literature search identified 4725 articles of which 12 studies met the inclusion criteria (figure 1). Among the included studies, nine provided data on anatomical outcome[4-7, 12, 16-19] and nine provided data on clinical outcome[4-7, 10-12, 18, 19] in CAD patients 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 eight of the nine 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 CAD patients 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 suffered a stroke (one fatal and one capsular stroke in one study[10] and one nonfatal

ischaemic stroke in another study[19]) during follow-up (table 5). Only two studies compared clinical outcome in CAD patients with and without DA.[7, 11]; no strokes occurred in either group (table 5).

DISCUSSION

In the prospective CADISS study our data demonstrates that DA is a relatively common sequel to extracranial vessel dissection, have 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 suggests 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 suggests 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, analysed 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, take 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 significantly to the work.

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Data Monitoring Committee: Gary A Ford, University of Newcastle (Chair); Philip M W Bath, University of Nottingham; Chris Weir, University of Glasgow.

Adjudication Committee: Prof Lalit Kalra, Kings College London (chair); Dr Denis Briley, Stoke Mandeville Hospital; Dr Ajay Bhalla, Guys and St Thomas NHS Trust

CADISS Participating Centres (Number of enrolled per centre; Principal Investigator)

UK total: 232

Aberdeen Royal Infirmary, Aberdeen (12; John Reid), Aintree University Hospital, Liverpool (13; Raj Kumar), Airedale General Hospital, Keighley (3; Samantha Mawer, Matthew Smith), Brighton and Sussex University Hospital, Brighton (3; Khalid Ali), Charing Cross Hospital, London (5; Pankaj Sharma), Cheltenham General and Gloucester Royal Hospitals, Cheltenham and Gloucester (1; Dipankar Dutta), Derriford Hospital, Plymouth (1; Azlisham Mohd Nor), Frenchay Hospital, Bristol (1; Rose Boswell, Neil Baldwin), Guy's and St Thomas' (6; Anthony Rudd), Heartlands Hospital, Birmingham (0; David Stanley), Hope Hospital), Kent and Canterbury Hospital, Canterbury (3; Isle Burger), King's College Hospital, London (9; Lalit kalra), Leeds General Hospital, Leeds (6; Ahamed Hassan), Musgrove Park Hospital, Taunton (1; Christopher Price), Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne (5; Anand Dixit), Ninewells Hospital, Dundee (6; Ronald MacWalter), Northwick Park, Harrow (1; David Cohen), Pinderfields General Hospital, Wakefield (2; Richard Davey), Queen Elizabeth Hospital, Gateshead (1; Tim Cassidy), Queen Elizabeth Queen Mother Hospital, Margate (6; Gunarathnam Gunathilagan), Royal Bournemouth Hospital, Bournemouth (2; Damian Jenkinson), Royal Cornwall Hospitals NHS Trust, Truro (5; Frances Harrington), Royal Devon and Exeter Hospital, Exeter (7; Martin James), Royal Hallamshire Hospital, Sheffield (15; Graham Venables), Royal Hampshire Hospital, Winchester (1; Nigel Smyth), Royal Preston Hospital, Preston (1; Hedley Emsley), Royal United Hospital, Bath (4; Louise Shaw), Southampton General Hospital, Southampton (2; Joanna Lovett), Southend Hospital, Southend (11; Paul Guyler), St George's Hospital, London (58; Hugh Markus), Royal London Hospital (1; Patrick Gompertz), Torbay Hospital, Torbay (2; Debs Kelly, Isam Salih), University Hospital North Staffordshire, Stoke-on Trent (9; Brendan Davies), University Hospital Wales, Cardiff (1; Hamsaraj Shetty), University Hospitals of Leicester (2; Amit Mistri), Western General Hospital, Edinburgh 3 (Malcolm Macleod, Bridget Colam, Rustam Al-Shahi Salman), William Harvey Hospital, Ashford (2; David Hargroves), Yeovil District Hospital (2; Khalid Rashed) Frimley Park Hospital, Frimley (2; Brian Clarke), Watford General Hospital, Watford, (18; David Collas).

Australia total: 18

Austin Hospital, Melbourne (2; Richard Gerraty), Gosford Hospital, Gosford (3; Jon Sturm), John Hunter Hospital, New Lambton (4: Chris Levi), Royal Adelaide Hospital, Adelaide (6; Tim Kleinig), Royal Brisbane and Women's Hospital, Brisbane (1; Andrew Wong), Royal Melbourne Hospital, Melbourne (1; Peter Hand), Royal Prince Alfred Hospital (1; Candice Delcourt).

REFERENCES

1. Debette S, Leys D. Cervical-artery dissections: predisposing factors, diagnosis, and outcome. Lancet Neurol 2009;8:668-678.
2. Mokri B, Sundt TM, Jr., Houser OW, Piepgras DG. Spontaneous dissection of the cervical internal carotid artery. Ann Neurol 1986;19:126-138.
3. Sturzenegger M. Spontaneous internal carotid artery dissection: early diagnosis and management in 44 patients. J Neurol 1995;242:231-238.
4. Guillon B, Brunereau L, Biousse V, Djouhri H, Levy C, Bousser MG. Long-term follow-up of aneurysms developed during extracranial internal carotid artery dissection. Neurology 1999;53:117-122.
5. Djouhri H, Guillon B, Brunereau L, et al. MR angiography for the long-term follow-up of dissecting aneurysms of the extracranial internal carotid artery. AJR Am J Roentgenol 2000;174:1137-1140.
6. Touze E, Randoux B, Meary E, Arquizan C, Meder JF, Mas JL. Aneurysmal forms of cervical artery dissection : associated factors and outcome. Stroke 2001;32:418-423.
7. Pelkonen O, Tikkakoski T, Leinonen S, Pyhtinen J, Lepojarvi M, Sotaniemi K. Extracranial internal carotid and vertebral artery dissections: angiographic spectrum, course and prognosis. Neuroradiology 2003;45:71-77.
8. Rizzo L, Crasto SG, Savio D, et al. Dissection of cervicocephalic arteries: early diagnosis and follow-up with magnetic resonance imaging. Emerg Radiol 2006;12:254-265.
9. Lee VH, Brown RD, Jr., Mandrekar JN, Mokri B. Incidence and outcome of cervical artery dissection: a population-based study. Neurology 2006;67:1809-1812.
10. Benninger DH, Gandjour J, Georgiadis D, Stockli E, Arnold M, Baumgartner RW. Benign long-term outcome of conservatively treated cervical aneurysms due to carotid dissection. Neurology 2007;69:486-487.
11. Wessels T, Mosso M, Krings T, Klotzsch C, Harrer JU. Extracranial and intracranial vertebral artery dissection: long-term clinical and duplex sonographic follow-up. J Clin Ultrasound 2008;36:472-479.
12. Daou B, Hammer C, Chalouhi N, et al. Dissecting pseudoaneurysms: predictors of symptom occurrence, enlargement, clinical outcome, and treatment. J Neurosurg 2016:1-7.
13. Markus HS, Hayter E, Levi C, Feldman A, Venables G, Norris J. Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): a randomised trial. Lancet Neurol 2015;14:361-367.
14. Cervical Artery Dissection in Stroke Study Trial I. Antiplatelet therapy vs. anticoagulation in cervical artery dissection: rationale and design of the Cervical Artery Dissection in Stroke Study (CADISS). Int J Stroke 2007;2:292-296.
15. Kennedy F, Lanfranconi S, Hicks C, et al. Antiplatelets vs anticoagulation for dissection: CADISS nonrandomized arm and meta-analysis. Neurology 2012;79:686-689.
16. Mokri B. Traumatic and spontaneous extracranial internal carotid artery dissections. J Neurol 1990;237:356-361.
17. Leclerc X, Lucas C, Godefroy O, et al. Helical CT for the follow-up of cervical internal carotid artery dissections. AJNR Am J Neuroradiol 1998;19:831-837.
18. Foreman PM, Griessenauer CJ, Falola M, Harrigan MR. Extracranial traumatic aneurysms due to blunt cerebrovascular injury. J Neurosurg 2014;120:1437-1445.
19. Kobayashi N, Murayama Y, Yuki I, et al. Natural course of dissecting vertebrobasilar artery aneurysms without stroke. AJNR Am J Neuroradiol 2014;35:1371-1375.

Table 1 Number (%) of patients with dissecting aneurysm at baseline and 3 months in CADISS

	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: DA = dissecting aneurysm; ICA = internal carotid artery; VA = vertebral artery.

Table 2 Characteristics of patients with and without dissecting aneurysm at baseline or 3 months in CADISS

Characteristic[a]	DA at baseline or 3 months			No DA at any time point			*p* value[b]
	All (48)	ICA (27)	VA (21)	All (216)	ICA (96)	VA (120)	
Age, years	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 days)	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: DA = dissecting aneurysm; ICA = internal carotid artery; VA = vertebral artery.

[a] Data are presented as numbers (%), except for age, which is presented as mean (SD).

[b] *p* value for difference in baseline characteristic for all patients without dissecting aneurysm versus all patients with dissecting aneurysm at any point.

Table 3 Associations of antiplatelet and anticoagulant therapy with persistence of dissecting aneurysm and development of new dissecting aneurysm at 3 months follow-up in CADISS

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; DA = dissecting aneurysm; 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.

Table 4 Previous studies of anatomical outcome of dissecting aneurysms due to cervical artery dissection in medically treated patients

Reference	Study design	Imaging modality for DA diagnosis	Mean time (months) between repeated imaging[a]	Patient population	Dissecting aneurysms			Angiographic findings for ICA[b]				Angiographic findings for VA[b]			
					Total DA	ICA	VA	Unchanged	Resolved	Decreased	Enlarged	Unchanged	Resolved	Decreased	Enlarged
16	Retrospective[c]	CA/DSA	64	Spontaneous	18	20	0	6 (33)	4 (22)	8 (45)	0				
			40	Traumatic	12	14[d]	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%)[e]	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[f]	NA	NA	60 (56)[g]	33 (30)[g]	0	15 (14)[g]	–	–	–	–
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 = computed tomography angiography; DSA = digital subtraction angiography; ICA = internal carotid artery; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; NA = not available; VA = vertebral artery.

[a] In months.
[b] Data are reported as number (%) of dissecting aneurysms that were unchanged or had resolved, decreased, or enlarged during follow-up.
[c] 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.
[d] Four DAs were eliminated by resection.
[e] One patient who had artery ligated was omitted from analysis.
[f] Including 18.3% intracranial dissecting aneurysms and 20.8% of patients received an intervention other than medical treatment.
[g] Internal carotid artery and vertebral artery dissecting aneurysms combined.

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

Reference	Study design	Mean age (years)	Time since symptom onset	Mean follow-up (months)	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 respectively 79% and 21% of patients	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 respectively 55% and 45% of patients	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	Non-stroke; 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: CAD = cervical artery dissection; ICA = internal carotid artery; NA = not available; VA = vertebral artery.

[a] Number of cervical artery dissection patients with/without dissecting aneurysm.

[b] One patient who died at 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] Internal carotid artery and vertebral artery dissecting aneurysm patients combined. Only patients not undergoing neurobiological or surgical intervention included.

FIGURE LEGEND

Figure 1. Flow chart of study selection.

Abbreviations: CAD = cervical artery dissection; DA = dissecting aneurysm.