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Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): a randomised trial
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Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): a randomised trial

*The CADISS trial investigators**

Summary

Background Extracranial carotid and vertebral artery dissection is an important cause of stroke, especially in young people. In some observational studies it has been associated with a high risk of recurrent stroke. Both antiplatelet drugs and anticoagulant drugs are used to reduce risk of stroke but whether one treatment strategy is more effective than the other is unknown. We compared their efficacy in the Cervical Artery Dissection in Stroke Study (CADISS), with the additional aim of establishing the true risk of recurrent stroke.

Methods We did this randomised trial at hospitals with specialised stroke or neurology services (39 in the UK and seven in Australia). We included patients with extracranial carotid and vertebral dissection with onset of symptoms within the past 7 days. Patients were randomly assigned (1:1) by an automated telephone randomisation service to receive antiplatelet drugs or anticoagulant drugs (specific treatment decided by the local clinician) for 3 months. Patients and clinicians were not masked to allocation, but investigators assessing endpoints were. The primary endpoint was ipsilateral stroke or death in the intention-to-treat population. The trial was registered with EUDract (2006-002827-18) and ISRN (CTN44555237).

Findings We enrolled 250 participants (118 carotid, 132 vertebral). Mean time to randomisation was 3·65 days (SD 1·91). The major presenting symptoms were stroke or transient ischaemic attack (n=224) and local symptoms (headache, neck pain, or Horner's syndrome; n=26). 126 participants were assigned to antiplatelet treatment versus 124 to anticoagulant treatment. Overall, four (2%) of 250 patients had stroke recurrence (all ipsilateral). Stroke or death occurred in three (2%) of 126 patients versus one (1%) of 124 (odds ratio [OR] 0·335, 95% CI 0·006–4·233; p=0·63). There were no deaths, but one major bleeding (subarachnoid haemorrhage) in the anticoagulant group. Central review of imaging failed to confirm dissection in 52 patients. Preplanned per-protocol analysis excluding these patients showed stroke or death in three (3%) of 101 patients in the antiplatelet group versus one (1%) of 96 patients in the anticoagulant group (OR 0·346, 95% CI 0·006–4·390; p=0·66).

Interpretation We found no difference in efficacy of antiplatelet and anticoagulant drugs at preventing stroke and death in patients with symptomatic carotid and vertebral artery dissection but stroke was rare in both groups, and much rarer than reported in some observational studies. Diagnosis of dissection was not confirmed after review in many cases, suggesting that radiographic criteria are not always correctly applied in routine clinical practice.

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Introduction

Cervical artery dissection accounts for only 1–2% of all ischaemic strokes, but in young and middle-aged people it accounts for 10–25% of strokes.[1] Some studies suggest a significantly increased risk of stroke in patients presenting with dissection either with local symptoms, such as headache and Horner's syndrome, or with stroke or transient ischaemic attack, with estimates of the risk of secondary stroke after presentation of 15–20%,[2–4] although other studies have reported a much lower proportion.[5] These studies suggested that most strokes occurred soon after initial onset of symptoms. Embolism from thrombus forming at the dissection site is thought to play the major part in stroke pathogenesis.[6] This suggestion is supported by transcranial Doppler studies[7,8] showing cerebral microemboli soon after dissection, and by the distribution of infarcts after dissection, which suggests an embolic pattern.[9]

The risk of early recurrence of stroke has led many clinicians to advocate the use of anticoagulation from presentation until 3 or 6 months after dissection. However others believe that antiplatelet drugs might be sufficient.[10] Anticoagulants might prevent embolism from a fresh thrombus but they are also more hazardous than antiplatelet drugs and can result in extension of the intramural haemorrhage, which occurs in a third of patients according to MRI.[11] No data exist from randomised controlled trials assessing the relative efficacy of the two treatments.

The Cervical Artery Dissection In Stroke Study (CADISS) was established to compare the effectiveness of antiplatelet drugs with anticoagulant drugs for the prevention of recurrent stroke in patients with carotid and vertebral dissection. It was established as a phase 2 feasibility trial with a planned sample size of 250 to enable accurate estimation of the rate of recurrent stroke and thereby samples sizes for a definitive phase 3 trial to be calculated.

Methods

Study design and participants

We did this randomised open-label parallel randomised trial at hospitals with specialised stroke or neurology services in the UK (n=39) and Australia (n=7). The full study protocol has been previously published.[12]

We enrolled patients from inpatient or outpatient services who had extracranial carotid or vertebral artery dissection with onset of symptom within the past 7 days, and imaging evidence of definite or probable dissection. Patients who had had stroke or transient ischaemic attack within the past 7 days were eligible. Imaging evidence of dissection had to be by MRI or magnetic resonance angiography, CT angiography, or intra-arterial angiography: although patients could be randomised on the basis of ultrasound alone, subsequent confirmation with MRI, magnetic resonance angiography, or CT angiography was required.

Exclusion criteria were: intracranial cerebral artery dissection; contraindications to either antiplatelet or anticoagulation drugs, including active peptic ulceration or bleeding peptic ulcer within 1 year; use of antiplatelet or anticoagulants drugs for other reasons (eg, prosthetic heart valves) for which the treatment cannot be replaced with either antiplatelet or anticoagulant drugs; and pregnancy.

The study was approved by ethics committees of all participating centres in Australia and the UK. All patients gave written informed consent before enrolment.

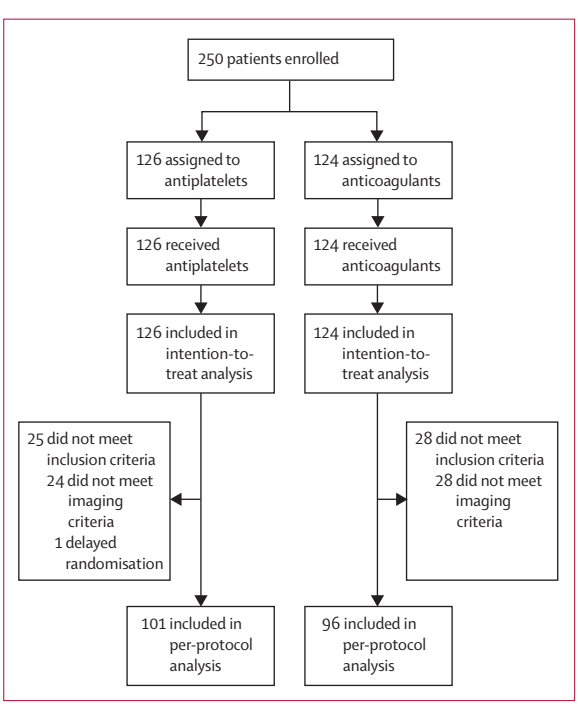

Figure: **Trial profile**

Randomisation and masking

Patients were randomly assigned (1:1) to either antiplatelet treatment or anticoagulation treatment by an automated telephone randomisation service provided by the University of Aberdeen (Aberdeen, UK). Both patients and clinicians were aware of treatment allocation, but an adjudication committee that assessed all primary and secondary endpoints were masked to treatment allocation.

Procedures

The choice of antiplatelet drug or anticoagulant drug was at the discretion of the local physician. Antiplatelet treatments included aspirin, dipyridamole, or clopidogrel alone or in combination. For patients assigned to anticoagulation, treatment with heparin (either unfractionated heparin or a therapeutic dose of low-molecular-weight heparin) was followed by warfarin, aiming for an international normalised ratio of 2–3. Novel oral anticoagulants were not used. Low-dose heparin prophylaxis for prevention of deep-vein thrombosis was not a contraindication, but its use was recorded. Such prophylaxis could be continued after randomisation in the antiplatelet group at the discretion of the local clinician.

Patients were followed up at 3 months after randomisation, when data for outcome and occurrence of recurrent stroke and transient ischaemic attack were recorded. Repeat imaging with magnetic resonance angiography or CT angiography to assess vessel recanalisation was done whenever possible at the 3-month follow up visit.

Outcomes

The primary endpoint was ipsilateral stroke or death (any cause) within 3 months of randomisation in the intention-to-treat population. For vertebral dissection, an ipsilateral event was defined as a recurrent event in the vertebrobasilar territory. Secondary endpoints were: ipsilateral transient ischaemic attack (including amaurosis fugax), stroke, or death (any cause); any stroke or death (any cause); any stroke, death, or major bleeding; any stroke; any transient ischaemic attack (including amaurosis fugax) or stroke; death; residual stenosis (>50%); and major bleeding.

Major bleeding was defined according to the International Society on Thrombosis and Haemostasis definition:[13] fatal bleeding or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial,

or intramuscular with compartment syndrome, or bleeding causing a fall in haemoglobin concentration of 1·24 units or more, or leading to transfusion of two or more units of whole blood or red cells. Stroke was defined by the WHO definition[14] as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 h or leading to death, with no apparent cause other than that of vascular origin.

Statistical analysis

We planned to enrol 250 participants on the basis of observational studies.[2–4] We did no interim analyses.

All enrolled patients were included in the intention-to-treat population. We also did a per-protocol analysis, which excluded any patient who did not meet inclusion criteria for any reason, including failure to confirm diagnosis of dissection on central review of imaging. We calculated exact CIs with the binomial (Clopper-Pearson) exact method. We compared the treatment effect in each group by exact logistic regression (Stata, version 13). We did the other analyses with SPSS (version 20).

We did power calculations to estimate the sample size needed for a definitive phase 3 trial with an online power calculator. These calculations were based on the combined endpoint of stroke, death, and major bleeding, with a power of 0·8 and a p value of 0·05.

This trial is registered with EudraCT (2006-002827-18) and ISRN (CTN44555237) and was adopted by the English National Institute for Health Research Clinical Research Network (2181).

Role of the funding source

The funder had no role in study design, data collection, analysis, or interpretation, writing of the report, or the decision to submit for publication. All authors had full access to all the data in the study. The final decision to submit the report for publication was made by HSM.

Results

We recruited 250 patients between Feb 24, 2006, and June 17, 2013. 118 had carotid dissection and 132 had vertebral arterial dissection. Mean time to randomisation was 3·65 days (SD 1·91). 174 (70%) of participants were male. Mean age was 49 years (SD 12, range 18–87). 126 participants were randomly assigned to antiplatelet treatment and 124 to anticoagulation treatment (figure). The major presenting symptoms were cerebral ischaemic in 224 patients (195 ischaemic stroke, 29 transient ischaemic attack) and local symptoms in 26 patients (22 headache, 22 neck pain, four Horner's syndrome). Table 1 shows baseline characteristics. All patients were followed up for 3 months.

In the antiplatelet group, 28 (22%) of 126 patients received aspirin alone, 42 (33%) received clopidogrel alone, one (1%) received dipyridamole alone, 35 (28%) received aspirin and clopidogrel, and 20 (16%) received aspirin and dipyridamole. In the anticoagulant group, 112 (90%) of 124 patients received heparin and warfarin and 12 (10%) received warfarin alone.

Original brain imaging and angiographic imaging was reviewed for all patients throughout the study and before the database was locked. Dissection was confirmed for 198 patients (102 in the antiplatelet group, 96 in the anticoagulant group). For one patient in the antiplatelet group, although recruited within 7 days, randomisation was not done until day 9 because of a technical error. Therefore the per-protocol analysis included 197 patients (101 in the antiplatelet group, 96 in the anticoagulant group).

For the **online power calculator** see https://www.sealedenvelope.com/power/binary-superiority/

	Intention-to-treat population		Per-protocol population	
	Antiplatelet group (n=126)	Anticoagulant group (n=124)	Antiplatelet group (n=101)	Anticoagulant group (n=96)
Age (years)	49·3 (12)	49·2 (12)	48·5 (12)	48·1 (11)
Men	87 (69%)	87 (70%)	69 (68%)	66 (69%)
Site of dissection				
Internal carotid artery	58 (46%)	60 (48%)	51 (50%)	47 (49%)
Vertebral artery	68 (54%)	64 (52%)	50 (50%)	49 (51%)
Presenting signs and symptoms				
Amaurosis fugax	4 (3%)	5 (4%)	4 (4%)	4 (4%)
Retinal infarction	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Transient ischaemic attack	27 (21%)	20 (16%)	20 (20%)	15 (16%)
Ischaemic stroke	93 (74%)	101 (81%)	74 (73%)	77 (80%)
Headache	84 (67%)	83 (67%)	68 (67%)	68 (71%)
Neck pain	57 (45%)	63 (51%)	41 (41%)	51 (53%)
Horner's syndrome	26 (21%)	34 (27%)	24 (24%)	29 (30%)
Time between symptoms and randomisation (days)	3·9 (1·8)	3·4 (2·0)	3·8 (1·8)	3·3 (2·1)
Modified Rankin score	2·1 (1·5)	2·1 (1·5)	2·1 (1·6)	2·2 (1·5)
Received stroke thrombolysis	12 (10%)	10 (8%)	10 (10%)	8 (8%)
Risk factors				
Treated hypertension	29 (23%)	26 (21%)	21 (21%)	19 (20%)
Diabetes	5 (4%)	5 (4%)	3 (3%)	3 (3%)
Treated hyperlipidaemia	16 (13%)	19 (15%)	12 (12%)	11 (12%)
Ever smoked	63 (50%)	66 (53%)	52 (52%)	51 (53%)
Migraine	20 (16%)	25 (20%)	15 (15%)	22 (23%)
History of trauma to head or neck within past 28 days	32 (25%)	21 (17%)	26 (26%)	16 (17%)
Systolic blood pressure (mm Hg)	137·7 (20·9)	135·9 (19·9)	137·78 (20·3)	135·1 (19·5)
Diastolic blood pressure (mm Hg)	81·9 (12·2)	84·0 (15·1)	82·2 (12·1)	84·2 (15·0)
Cholesterol concentration (mmol/L)*	5·22 (1·14)	5·16 (1·32)	5·21 (1·19)	5·18 (1·38)
Diagnostic imaging				
CT	110 (87%)	105 (85%)	87 (87%)	82 (85%)
MRI	103 (82%)	93 (75%)	80 (79%)	70 (73%)
Angiography				
Any	122 (97%)	120 (97%)	99 (98%)	95 (99%)
Magnetic resonance angiography	94 (75%)	83 (67%)	73 (72%)	66 (69%)
CT angiography	54 (43%)	58 (47%)	47 (47%)	46 (48%)
Digital subtraction angiography	1 (1%)	3 (2%)	1 (1%)	3 (3%)

Data are mean (SD) or n (%). *Measured for 101 participants in the antiplatelet group and 108 participants in the anticoagulant group.

Table 1: **Baseline characteristics**

	Intention-to-treat population				Per-protocol population			
	Antiplatelet group (n=126)	Anticoagulant group (n=124)	OR (95% CI)*	p value	Antiplatelet group (n=101)	Anticoagulant group (n=96)	OR (95% CI)*	p value
Ipsilateral stroke or death	3 (2%)	1 (1%)	0·335 (0·006–4·233)	0·63	3 (3%)	1 (1%)	0·346 (0·006–4·390)	0·66
Secondary endpoints								
Any stroke or death	3 (2%)	1 (1%)	0·335 (0·006–4·233)	0·63	3 (3%)	1 (1%)	0·346 (0·006–4·390)	0·66
Any stroke, death, or major bleed	3 (3%)	2 (2%)	0·673 (0·055– 5·983)	1·00	3 (3%)	2 (2%)	0·696 (0·057–6·220)	1·00
Any stroke	3 (2%)	1 (1%)	0·335 (0·006–4·233)	0·63	3 (3%)	1 (1%)	0·346 (0·006–4·390)	0·66
Ipsilateral stroke, TIA, or death	4 (3%)	5 (4%)	1·280 (0·268–6·614)	0·98	4 (4%)	4 (4%)	1·054 (0·190–5·835)	1·00
Any stroke or TIA	5 (4%)	5 (4%)	1·017 (0·228–4·540)	1·00	5 (5%)	4 (4%)	0·836 (0·161–4·015)	1·00
Major bleeding	0 (0%)	1 (1%)	..	..	0 (0%)	1 (1%)	..	..
Death	0 (0%)	0 (0%)	..	..	0 (0%)	0 (0%)	..	..

Data for presence of residual stenosis (>50%) at 3 months have not yet been analysed. OR=odds ratio. TIA=transient ischaemic attack. *Tested with exact logistic regression.

Table 2: **Outcomes within 3 months**

	Antiplatelet group (n=126)	Anticoagulant group (n=124)
Abdominal pain	0 (0%)	1 (1%)
Abnormal liver function test	0 (0%)	1 (1%)
Allergic reaction	1 (1%)	0 (0%)
Chest pain	0 (0%)	1 (1%)
Diplopia	1 (1%)	0 (0%)
Dizziness	0 (0%)	1 (1%)
Haematuria	0 (0%)	1 (1%)
Haemoptysis	0 (0%)	1 (1%)
Headache	4 (3%)	3 (2%)
Hip pain	0 (0%)	1 (1%)
Hydrocephalus	0 (0%)	1 (1%)
Myocardial infarction	1 (1%)	0 (0%)
Nausea or vomiting	3 (2%)	1 (1%)
Neck pain	0 (0%)	1 (1%)
Numbness	0 (0%)	1 (1%)
Ophthalmic nerve neuralgia	1 (1%)	0 (0%)
Pneumonia	1 (1%)	1 (1%)
Seizure	0 (0%)	2 (2%)
Subarachnoid haemorrhage	0 (0%)	1 (1%)
Vision loss	0 (0%)	1 (1%)
Worsening of ataxia	1 (1%)	0 (0%)
Worsening of Horner's syndrome	0 (0%)	1 (1%)

Four patients (two in each treatment group) had two adverse events; no patient had more than two adverse events.

Table 3: **Adverse events**

Overall, stroke recurred in four (2%) of 250 patients in the intention-to-treat population: three in the antiplatelet group versus one in the anticoagulant group, all ipsilateral (appendix p 2). All recurrent strokes occurred in patients in whom the presenting symptom was stroke (four [2%] of 194 patients; three carotid, one vertebrobasilar).No deaths occurred, therefore the primary endpoint of ipsilateral stroke or death occurred in three (2%) of 126 patients in the antiplatelet group versus one (1%) of 124 in the anticoagulant group (odds ratio 0·335, 95% CI 0·006–4·233; p=0·63; table 2). In the per-protocol population, stroke recurred in four (2%) of 196 patients overall, and in four (3%) of 151 who presented with stroke (appendix).

See Online for appendix

For the intention-to-treat population, ipsilateral transient ischaemic attack occurred in one (1%) of 126 patients in the antiplatelet group versus four (3%) of 124 patients in the anticoagulant group (one [1%] of 101 *vs* three [3%] of 96 in the per-protocol population). Other transient ischaemic attack occurred in only one patient in the antiplatelet group, in both the intention-to-treat and per-protocol populations (appendix).

None of the secondary endpoints differed significantly between treatment groups. Results in the intention-to-treat and per-protocol populations were much the same (table 2).

Table 3 shows adverse events. One major bleed occurred in the anticoagulant group (none in the antiplatelet group), in a patient with vertebral dissection with extension intracranially who developed a subarachnoid haemorrhage. This patient presented with headache with no focal neurological symptoms and CT brain imaging showed intraventricular blood. Two minor bleeds occurred in the anticoagulant group (one haematuria and one haemoptysis), and none in the antiplatelet group.

To establish whether recurrent events might have occurred before recruitment and randomisation, we did a post-hoc analysis of patients presenting with stroke in whom previous transient ischaemic attack or minor stroke had occurred. In the intention-to-treat population, nine such patients were present in the anticoagulant group versus ten in the antiplatelet group (seven *vs* seven in the per-protocol population). The mean time between previous symptoms and subsequent stroke was 3·4 days (SD 5·5, range 0·04–21; median 1 day, IQR 0·25–4·0) in the intention-to-treat population, and 3·9 days (SD 6·3, range 0·13–21; median 1 day, IQR 0·3–5·0) in the per-protocol population.

To assess the feasibility of a phase 3 trial, we did power calculations with the per-protocol data, and the composite outcome of stroke, death, or major bleeding (2·08%, 95% CI 0·25–7·32 in the anticoagulant group and 2·97%, 0·62–8·44 in the antiplatelet group). We calculated that a study with a power of 0·8 and significance level of 0·05 would require a sample size of 4876 in each group.

Discussion

The results of our study, to our knowledge the first randomised trial of antiplatelet treatment compared with anticoagulant treatment for extracranial carotid and vertebral artery dissection (panel), show that recurrent stroke at 3 months is rare, with no significant difference between the two treatments. Although more strokes occurred in the antiplatelet group than in the anticoagulant group, this difference was counterbalanced by one major subarachnoid haemorrhage in the anticoagulant group.

The risk of recurrent events was lower than that reported in some observational studies. One of the first studies,[2] which included 80 patients with carotid dissection (29 retrospectively and 51 prospectively recruited) reported recurrences in 17 (41%) of 41 patients presenting with transient ischaemic attack. In a prospective multicentre Canadian study,[3] in which follow-up data were available for 105 individuals, nine patients had stroke after presentation with either carotid or vertebral dissection, although five recurrences were before study enrolment; the time between enrolment and onset of symptoms was not documented. By contrast, a retrospective analysis[15] of data from 298 patients with carotid dissection, all treated with either antiplatelet or anticoagulant drugs, reported fewer recurrences: 0·3% had ischaemic stroke, 3·4% had transient ischaemic attack, and 1·0% had retinal ischaemia. New ischaemic events were significantly more common in patients with ischaemic events at onset (6·2%) than in patients with local symptoms or asymptomatic patients (1·1%). The results from the non-randomised part of CADISS[6] reported a similarly low proportion: two (2%) recurrent strokes occurred during 3-month follow-up of 87 individuals with both carotid and vertebral artery dissection; however, mean time from symptom onset was 10·8 days (SD 7·0, range 1–31). In a trial setting, patients might have been recruited after they had already had their recurrent stroke; however, few patients in our study had such symptoms, suggesting this effect was not the reason for the difference in recurrence of stroke in CADISS compared with previous observational studies.

Because recurrences were rare, any definitive study examining this question is likely to need a very large sample size. Power calculations based on the per-protocol data and using the endpoint of stroke, death, or major bleeding gave a required total sample size of almost 10 000 participants, which will be difficult to recruit. However, because the outcomes were rare, the 95% CIs for the endpoints were large and therefore the number of participants needed according to our calculation should be considered a rough estimate.

Diagnosis of dissection could not be centrally confirmed on imaging review in about a fifth of participants, despite evidence of dissection on angiographic imaging or cross-sectional imaging through the vessel wall. The failure to confirm diagnosis was mainly caused by two factors. First, imaging was of poor quality for some participants and it was impossible to be sure of the diagnosis. Second, central review of imaging suggested an alternative diagnosis in some patients for whom imaging was of adequate quality. The most common alternative diagnoses were atherosclerosis, an atretic rather than dissected vertebral artery, a narrowed artery without any definite evidence of dissection and, in one case, adherent thrombus without clear evidence of dissection.

Several radiographic features suggest dissection, including appearance of a flap, tapering stenosis or pseudoaneurysm on angiography, and imaging of the arterial wall showing intramural blood. The difficulties associated with diagnosis of dissection have been well-documented.[16] For imaging of the vessel, difficulties include limited spatial resolution, the tortuous course of arteries, variability in normal vessel calibre, presence of a thick bone covering, and adjacent veins. Imaging the vertebral arteries is more difficult than imaging the carotid arteries because of their smaller size, the fact that one is often atretic, and because flow-related enhancement of the vertebral plexus surrounding the artery can mimic intramural blood.[16] This greater difficulty in diagnosis of vertebral dissection was shown by the lower proportion of confirmed diagnoses for vertebral artery dissection (100 of 132) versus carotid dissection (98 of 118). However, the low proportion of confirmed diagnoses and variations between recruitment sites suggest that training and quality control need to be improved. We did not use prespecified imaging criteria; doing so might have improved the accuracy of diagnosis.

CADISS was designed as a pragmatic trial and therefore the choice of antiplatelet drugs was at the discretion of the clinician. Prescription of dual antiplatelet treatment for all patients might have improved efficacy. Another limitation is that many patients did not have imaging confirmation after central review; however, this shortcoming provides important information about routine clinical practice in the real world and a strength of the study was central review of imaging for all patients. Disease heterogeneity—eg, carotid versus vertebral dissection, or recent stroke versus local symptoms only—might have caused different groups to respond differently to treatments. Endpoints were too rare to assess such subgroups, but all recurrent strokes occurred in patients who had presented with stroke, consistent with previous data from observational studies,[15] suggesting this group are at the highest risk of recurrent event.

Panel: **Research in context**

Systematic review

We searched PubMed on Jan 23, 2015 with the term "(carotid artery OR vertebral artery OR cervical artery OR anterior circulation OR posterior circulation OR extracranial carotid artery) AND (dissection) AND (antiplatelet OR anticoagulant)". We found no previous randomised controlled trials examining whether antiplatelet or anticoagulant drugs are the better treatment.

Interpretation

This study was the first randomised controlled trial of dissection. We recruited 250 patients with extracranial carotid and vertebral artery dissection within 7 days of onset of symptoms and randomly assigned them to antiplatelet treatment or anticoagulant treatment for 3 months. We detected no difference between treatment groups for ipsilateral stroke or death. Only 2% of participants had recurrent stroke at 3 months, which is lower than that reported in previous studies. 20% of dissections were not confirmed after central review of imaging, suggesting criteria for diagnosis are not correctly applied in all cases.

Generalisability is important in any clinical trial. To estimate the proportion of patients presenting with dissection who were recruited to the study, during the early part of CADISS, patients who were not randomly assigned (either because they did not meet the inclusion criteria or because the clinician or patient did agree to randomisation) could be entered into a non-randomised arm.[6] During this period, while 77 participants were recruited to the randomised arm, 88 patients screened for inclusion were not randomly assigned and instead entered the observational arm. Reasons for exclusion from the randomised arm were: presentation after 7 days (n=53), contraindication to antiplatelet or anticoagulant drugs (n=12), already taking antiplatelet or anticoagulation drugs for other reasons (n=5), patient or physician unwilling to randomise (n=18).[6] These findings show that some patients (35 [21%] of 165) presenting within the 7-day window for inclusion in the randomised study were excluded.

In the observational arm of CADISS, stroke occurred in one (2%) of 59 patients treated with antiplatelet drugs, and in one (4%) of 28 patients treated with anticoagulant drugs. Some patients presenting with dissection, and perhaps particularly with very early, severe, recurrent stroke, might not have been included in either the observational or the randomised part of the study because they could not provide consent. Inclusion of patients within 24 h of onset of symptoms might have helped us to capture early recurrent strokes. However, some patients with dissection, particularly those with local symptoms, did not present on the day of onset. Furthermore, in the UK, a diagnosis of dissection might not be made until a couple of days after presentation because diagnostic angiographic or cross-sectional MRI is not always done at presentation. We therefore decided that a 7-day window would provide generalisable results, and also ensure that recruitment was feasible.

Contributors

HSM designed the study, obtained funding, was the principal investigator and overall study coordinator, analysed and interpreted data, and wrote the first draft. EH was a study coordinator, prepared data, and revised the report. CL was the Australian lead investigator, sat on the steering committee, interpreted data, and revised the report. AF prepared, analysed, and interpreted data. GV sat on the steering committee, interpreted data, and revised the report. JN designed the study, obtained funding, was coprincipal investigator, sat on the steering committee, and revised the report.

CADISS trial committees and investigators

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Participating centres (number of patients enrolled; principal investigator)

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Declaration of interests

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