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Antiplatelet Therapy vs Anticoagulation Therapy in Cervical Artery Dissection

The Cervical Artery Dissection in Stroke Study (CADISS) Randomized Clinical Trial Final Results

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IMPORTANCE Extracranial carotid and vertebral artery dissection is an important cause of stroke, particularly in younger individuals. In some but not all observational studies, it has been associated with a high risk of recurrent stroke. Both antiplatelet agents (APs) and anticoagulants (ACs) are used to reduce stroke risk, but whether 1 treatment strategy is more effective is unknown.

OBJECTIVE To determine whether AP or AC therapy is more effective in preventing stroke in cervical dissection and the risk of recurrent stroke in a randomized clinical trial setting. A secondary outcome was to determine the effect on arterial imaging outcomes.

DESIGN, SETTING, AND PARTICIPANTS Randomized, prospective, open-label international multicenter parallel design study with central blinded review of both clinical and imaging end points. Recruitment was conducted in 39 stroke and neurology secondary care centers in the United Kingdom and 7 centers in Australia between February 24, 2006, and June 17, 2013. One-year follow-up and analysis was conducted in 2018. Two hundred fifty participants with extracranial carotid and vertebral dissection with symptom onset within the last 7 days were recruited. Follow-up data at 1 year were available for all participants.

INTERVENTIONS Randomization to AP or AC (heparin followed by warfarin) for 3 months, after which the choice of AP and AC agents was decided by the local clinician.

MAIN OUTCOMES AND MEASURES The primary end point was ipsilateral stroke and death. A planned per protocol (PP) analysis was performed in patients meeting the inclusion criteria following central review of imaging to confirm the diagnosis of dissection. A secondary end point was angiographic recanalization in those with imaging confirmed dissection.

RESULTS Two hundred fifty patients were randomized (118 carotid and 132 vertebral), 126 to AP and 124 to AC. Mean (SD) age was 49 (12) years. Mean (SD) time to randomization was 3.65 (1.91) days. The recurrent stroke rate at 1 year was 6 of 250 (2.4%) on ITT analysis and 5 of 197 (2.5%) on PP analysis. There were no significant differences between treatment groups for any outcome. Of the 181 patients with confirmed dissection and complete imaging at baseline and 3 months, there was no difference in the presence of residual narrowing or occlusion between those receiving AP (n = 56 of 92) vs those receiving AC (n = 53 of 89) (P = .97).

CONCLUSIONS AND RELEVANCE During 12 months of follow-up, the number of recurrent strokes was low. There was no difference between treatment groups in outcome events or the rate of recanalization.

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Cervical artery dissection accounts for 1% to 2% of all ischemic strokes and is a common cause of stroke in young patients, in whom it accounts for 10% to 25%.[1] Some but not all studies have reported a markedly increased risk of stroke in patients presenting with dissection, with most strokes occurring soon after initial symptom onset. Embolism from thrombus forming at the dissection site is thought to play the major role in stroke pathogenesis.[2] This early recurrent stroke risk has led to clinicians routinely using antithrombotic therapy to reduce risk of recurrent stroke. Some have proposed using anticoagulants (ACs), suggesting they might be more effective at preventing embolism from fresh thrombus, but others argue antiplatelet agents (APs) are as effective and have lower risk of causing extension of the intramural hemorrhage and hemorrhage elsewhere. Until 2015, to our knowledge, there were no data from randomized clinical trials comparing the 2.

To our knowledge, the Cervical Artery Dissection in Stroke Study (CADISS) trial[3] provided the first randomized clinical trial data in carotid and vertebral dissection. Follow-up to the primary end point at 3 months found a low rate of recurrent stroke of only 1.6% at 3 months in the intention-to-treat (ITT) analysis and 2.0% when only patients meeting the inclusion criteria were included.[4] There was no difference between event rates in patients treated with AC or AP. The follow-up continued to 1 year, and here, we present the final results including the 1-year follow-up data. In addition, repeated angiographic imaging was performed at 3 months, and we present these results, comparing the rate of recanalization according to treatment arm.

Key Points

Question What is the recurrent stroke risk after carotid and vertebral artery dissection, and are antiplatelets or anticoagulants more effective at reducing this risk?

Findings In this randomized clinical trial, risk of recurrent stroke at 1 year was 2.5%, and there was no difference in recurrence rates or rates of angiographic recanalization with antiplatelets or anticoagulants.

Meaning The risk of recurrent stroke after carotid and vertebral dissection is low; there was no evidence that antiplatelets or anticoagulants were more effective at reducing this risk.

Methods

The CADISS trial was a randomized, prospective, open-label international multicenter parallel design study comparing AP with AC for patients with carotid and vertebral dissection. Both the full study protocol[3] and the results of the primary end point analysis to 3 months have been previously published.[4]

Recruitment was via inpatient or outpatient services in hospitals with specialized stroke/neurology services in United Kingdom and Australia. 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 experienced stroke or transient ischemic attack (TIA) within the last 7 days, they were eligible even if this was preceded by local symptoms with onset more than 7 days. Imaging evidence of definite or probable dissection had to be on magnetic resonance imaging or angiography (MRI/MRA), computed tomography angiography (CTA), or intra-arterial angiography, although a patient could be randomized on ultrasonography alone, but in such cases, subsequent MRI/MRA or CTA confirmation was required.

Exclusion criteria were refusal to consent; intracranial cerebral artery dissection; contraindications to AP or AC therapy including active peptic ulceration or bleeding peptic ulcer within 1 year; and patients already taking AP or AC for other reasons.

Treatments

Patients were randomized 1-to-1 to either AP or AC therapy for at least 3 months. It was a pragmatic treatment trial, and the choice of AP agent(s) or AC was at the choice of the local physician. In patients randomized to AP, this could include aspirin, clopidogrel, or dipyridamole or in dual combination. For patients randomized to AC, the recommended regimen was heparin (either unfractionated heparin or a therapeutic dose of low-molecular-weight heparin) followed by warfarin aiming for an international normalized ratio in the range 2 to 3. Novel oral anticoagulants were not used. Treatment was open label. After the 3-month treatment period, antithrombotic treatment was at the choice of the treating clinician. Low-dose heparin prophylaxis for prevention of deep venous thrombosis was allowed, but use was recorded.

Randomization and Masking

Randomization was provided via an automated 24-hour telephone randomization service provided by the University of Aberdeen, Scotland. Once randomized into the study, all patients were included in an ITT analysis.

The trial design was open, and both patients and clinicians were aware of treatment allocation. However, an adjudication committee assessed all primary end points (stroke) and secondary end points blinded to treatment arm.

Follow-up

Patients were seen in person at 3 months postrandomization for follow-up. Repeated clinical imaging with MRA or CTA was performed whenever possible at the 3-month follow-up. Each center performed imaging in line with their own standard dissection protocols. Telephone follow-up was performed at 6 and 12 months by a physician from the coordinating center at St George's Hospital in London. Australian telephone follow-up was performed by the Australian coordinating center in Newcastle, New South Wales, Australia.

In addition to review of imaging to assess eligibility, angiographic images at baseline and 3 months were reviewed in those patients with baseline imaging appearances confirming dissection by a consultant neuroradiologist (J.M.) who was blinded to treatment allocation and clinical details. The presence of stenosis or occlusion, mural hematoma, luminal flap/double lumen, and dissecting aneurysm (pseudoaneurysm)

formation was recorded. Imaging features considered pathognomonic for acute arterial dissection on presenting CT or MRI were either (1) focal expansion of the vessel by mural hematoma, (2) mural hematoma without vessel expansion but with luminal narrowing, or (3) differential perfusion of 2 lumina separated by a flap. Definite dissection had to show 1 of these pathognomonic features. Probable was when there were no pathognomonic features but features suggestive of a likely diagnosis of dissection, such as a string or beaded appearance or a focal occlusion at an anatomically typical site, with no evidence of atheromatous disease elsewhere.

Narrowing was determined by visual inspection only and defined as any reduction in caliber of the artery lumen when compared with a normal adjacent segment. Because most internal carotid artery dissections occur at or just beneath the skull base, the vessel segment below this but above the carotid bulb was used for reference. If the whole cervical segment was narrowed, the contralateral internal carotid artery was used as long as there was typical anterior circle of Willis anatomy, specifically, the presence of A1 segments of the anterior cerebral arteries bilaterally. At follow-up, complete recanalization was defined as the absence of any residual vessel abnormality. Partial recanalization was defined as a patent vessel lumen but with some residual narrowing or a dissecting aneurysm.

End Points

The primary end point was ipsilateral stroke or death (any cause) within 3 months from randomization. For vertebral dissection, an ipsilateral event was defined as a recurrent event in the vertebrobasilar territory.

Secondary end points were:

- Ipsilateral stroke or death (any cause) at 1 year
- Ipsilateral TIA (including amaurosis fugax), stroke, or death (any cause) at 3 and 12 months
- Any stroke or death (any cause) at 3 and 12 months
- Any stroke, death, or major bleeding at 3 and 12 months
- Any stroke at 3 and 12 months
- Any TIA (including amaurosis fugax) and stroke at 3 and 12 months
- Mortality at 3 and 12 months
- Presence of residual stenosis at 3 months
- Major bleeding

Major bleeding was defined using the International Society on Thrombosis and Hemostasis definition[5] as fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 1.24 units or more or leading to transfusion of 2 or more units of whole blood or red blood cells. Stroke was defined using the World Health Organization definition as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[6]

Trial Registration

The trial was registered with EUDract (2006-002827-18) and ISRN (CTN44555237). The formal trial protocols are available in Supplement 1. It was adopted by the English NIHR CRN Study ID 2181. Multicenter research ethics committee approval was obtained in the United Kingdom (MREC 04/Q0803/215) and Australia. All patients gave written informed consent.

Data Analysis

Analysis was performed according to a predefined statistical plan. Primary analysis was ITT. A per protocol (PP) analysis was also performed, which excluded patients not meeting inclusion criteria for any reason including failure to confirm diagnosis of dissection on central imaging review. Exact confidence intervals for proportions with events were calculated using the binomial (Clopper-Pearson) exact method. The treatment effect of AP vs AC was tested using exact logistic regression. Analysis was performed using SPSS Statistics, version 20 (IBM) and for exact logistic regression in Stata statistical software (StataCorp). The *P* value level of significance was less than .05, and *P* values were 2-sided.

Sample Size

The sample size was 250, which was planned to provide sufficient information for sample size estimates for a definitive phase 3 trial. No interim analyses were performed.

Results

A total of 250 patients were recruited from 39 centers in the United Kingdom and 7 centers in Australia between February 24, 2006, and June 17, 2013 (eFigure in Supplement 2). Presenting symptoms are shown in **Table 1**. Mean (SD) time to randomization was 3.65 (1.91) days. One hundred seventy-four patients were men (69.6%). Mean (SD) age was 49 (12) years (range, 18-87 years). One hundred eighteen patients were in the carotid and 132 in the vertebral artery distribution. One hundred twenty-six patients were randomized to AP and 124 were randomized to AC. The major presenting symptom was cerebral ischemia in 224 patients (194 with ischemic stroke, 1 with retinal infarction, and 29 with TIA including amaurosis fugax) and local symptoms in 26 patients (22 with headache and neck pain and 4 with Horner syndrome).

Treatment Received

In the AP arm, treatments received during the first 3 months were aspirin alone (n = 28; 22.2%), clopidogrel alone (n = 28; 22.2%), dipyridamole (n = 1; 0.8%), aspirin and clopidogrel (n = 35; 27.8%), and aspirin and dipyridamole (n = 20; 15.9%). In the AC arm, treatments received were heparin and warfarin (n = 112; 90.3%) and warfarin alone (n = 8; 9.7%). The number of patients receiving AC during the clinician-directed phase of treatment after 3 months fell at 6 months to 46 (18.4% of total recruits) and fell at 12 months to 15 (6.0%).

Per Protocol Population

Original brain and angiographic imaging were reviewed in all cases on an ongoing basis and completed prior to database locking. There were confirmatory features of a dissection in 198 patients (102 AP and 96 AC). In 1 additional patient random-

Table 1. Baseline Characteristics

Characteristic	No. (%)			
	Intention-to-Treat Population		Per Protocol Population	
	Antiplatelets (n = 126)	Anticoagulants (n = 124)	Antiplatelets (n = 101)	Anticoagulants (n = 96)
Age, mean (SD), y	49.3 (12)	49.2 (12)	48.5 (12)	48.1 (11)
Male	87 (69)	87 (70)	69 (68)	66 (69)
Site of dissection				
Internal carotid	58 (46)	60 (48)	51 (51)	47 (49)
Vertebral	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	1 (0.8)	0	1 (1.0)
TIA	27 (21)	20 (16)	20 (20)	15 (16)
Ischemic stroke	93 (74)	101 (82)	74 (73)	77 (80)
Headache	84 (67)	83 (67)	68 (67)	68 (71)
Neck pain	57 (45)	63 (51)	41 (41)	51 (53)
Horner syndrome	26 (20.6)	34 (27.4)	24 (24)	29 (30)
Time between symptoms and randomization, mean (SD), d	3.9 (1.8)	3.4 (2.0)	3.8 (1.8)	3.3 (2.1)
Modified Rankin score, mean (SD)	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 mellitus	5 (4)	5 (4)	3 (3)	3 (3)
Treated hyperlipidemia	16 (13)	19 (15)	12 (12)	11 (12)
Smoking history (ever smoked)	63 (50)	66 (53)	52 (52)	51 (53)
Migraine	20 (16)	25 (20)	15 (15)	22 (23)
History of trauma to head/neck within last 28 d	32 (25)	21 (17)	26 (26)	16 (17)
Blood pressure, mean (SD), mm Hg				
Systolic	137.7 (20.9)	135.9 (19.9)	137.78 (20.3)	135.1 (19.5)
Diastolic	81.9 (12.2)	84.0 (15.1)	82.2 (12.1)	84.2 (15.0)
Cholesterol, mean (SD), mg/dL[a]	201.54 (44.02)	199.23 (50.97)	201.16 (45.95)	200 (53.28)
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 (97)	95 (99)
MR	94 (75)	83 (67)	73 (72)	66 (69)
CT	54 (43)	58 (47)	47 (47)	46.0 (49)
Digital subtraction	1 (1)	3 (2)	1 (1)	3 (3)

Abbreviations: CT, computed tomography; MR, magnetic resonance; MRI, magnetic resonance imaging; TIA, transient ischemic attack.

SI conversion factor: To convert cholesterol to micromoles per liter, multiply by 0.0259.

[a] Cholesterol was measured for n = 101 in the antiplatelet arm and n = 108 in the anticoagulant arm.

ized to AP, although the patient was recruited within 7 days, because of a technical problem with the randomization process, randomization occurred on day 9. Therefore, the PP analysis included 197 patients (101 AP and 96 AC). The baseline characteristics in the 2 treatment arms are shown in Table 1.

End Points

Follow-up to 12 months was obtained in all patients. Events during follow-up are shown in **Table 2**. These are divided into those occurring within the first 3 months and those occurring during continued follow-up until 12 months. During the first 3 months, there were 4 recurrent strokes (1.6%), all ipsilateral, and no deaths. During extended follow-up between 3 and 12 months, there were 2 further strokes, both ipsilateral, and 1 death (in a patient who had experienced recurrent stroke in the first 3 months). In the ITT population, the overall recurrent stroke rate was 2.4% at 1 year. In the PP, the recurrent stroke rate was 2.5% at 1 year. All 6 events occurred in patients in whom the presenting symptom was stroke (4 carotid and 2 vertebrobasilar), giving an ITT recurrent rate of 3.1% in those presenting with stroke and 2.7% in those presenting with cerebral (including retinal) ischemia.

During 1-year follow-up in the ITT population, there were 4 primary end points (ipsilateral stroke) in the AP group and 2 in the AC group. Considering the combined end point of stroke, death, or major bleeding, there were 4 events in the AP arm and 3 in the AC arm. There were no significant differences between treatment groups for any end point on ITT analysis

Table 2. Events During Follow-up

	No.							
	Intention-to-Treat Analysis				Per Protocol Analysis			
	Antiplatelets (n = 126)		Anticoagulants (n = 124)		Antiplatelets (n = 101)		Anticoagulants (n = 96)	
Event	0-3 mo	3-12 mo	0-3 mo	3-12 mo	0-3 mo	3-12 mo	0-3 mo	3-12 mo
Ischemic stroke								
Ipsilateral	3	1	1	1	3	1	1	0
Other	0	0	0	0	0	0	0	0
TIA								
Ipsilateral	1	0	4	0	1	0	3	0
Other	1	0	0	1	1	0	0	1
Major bleeding	0	0	1	0	0	0	1	0
Death	0	1[a]	0	0	0	1[a]	0	0

Abbreviation: TIA, transient ischemic attack.

[a] Death owing to a fatal recurrent stroke in a patient who had a first recurrent stroke within the first 3-month follow-up period.

Table 3. Association Between Randomized Treatment and Risk of Having an Event

	As Randomized (ITT)				Per Protocol			
	No. (%)				No. (%)			
Event	Antiplatelets (n = 126)	Anticoagulants (n = 124)	OR (95% CI)[a]	*P* Value	Antiplatelets (n = 101)	Anticoagulants (n = 96)	OR (95% CI)[a]	*P* Value
Follow-up, 3 mo								
Ipsilateral stroke	3 (2.4)	1 (0.8)	0.42 (0.04-4.38)	.47	3 (3.0)	1 (1.0)	0.48 (0.04-5.28)	.55
Ipsilateral stroke or ipsilateral TIA	4 (3.2)	5 (4.0)	1.48 (0.37-5.90)	.58	4 (4.0)	4 (4.2)	1.23 (0.28-5.46)	.79
Any stroke or any TIA	5 (4.0)	5 (4.0)	1.12 (0.31-4.09)	.87	5 (5.0)	4 (4.2)	0.92 (0.23-3.72)	.91
Any stroke or death	3 (2.4)	1 (0.8)	0.42 (0.04-4.38)	.47	3 (3.0)	1 (1.0)	0.48 (0.04-5.28)	.55
Follow-up, 12 mo[b]								
Ipsilateral stroke	4 (3.2)	2 (1.6)	0.56 (0.10-3.21)	.51	4 (4.0)	1 (1.0)	0.32 (0.03-3.04)	.32
Ipsilateral stroke or ipsilateral TIA	5 (4.0)	6 (4.8)	1.36 (0.39-4.71)	.63	5 (5.0)	4 (4.2)	0.95 (0.23-3.83)	.94
Any stroke or any TIA	6 (4.8)	7 (5.65)	1.29 (0.41-4.03)	.66	6 (5.9)	5 (5.2)	0.95 (0.27-3.34)	.93
Any stroke or death	4 (3.2)	2 (1.6)	0.56 (0.10-3.21)	.51	4 (4.0)	1 (1.0)	0.32 (0.03-3.04)	.32

Abbreviations: ITT, intention to treat; OR, odds ratio; TIA, transient ischemic attack.

[a] Crude differences between treatment groups tested with Fisher exact test. Treatment effect of anticoagulants vs antiplatelets (reference) tested using a logistic regression model adjusted for sex and age at baseline (continuous).

[b] All events at 12 months are cumulative.

(**Table 3**), although analysis was limited by the few end points. Results from PP analysis are in Table 3. There were no significant differences between the 2 groups.

Angiographic Recanalization

Angiographic imaging with either CTA or MRA at baseline and at 3 months was available for 181 of 198 patients with radiologically confirmed dissection. Narrowing or occlusion at baseline occurred in 163 of 181 patients (81 AP and 82 AC). At follow-up, 61 of 181 patients (31 AP and 30 AC) did not have any abnormalities; 64 of 181 (34 AP and 30 AC) had residual irregularity or narrowing, 45 of 181 (22 AP and 23 AC) were occluded, and there were 29 of 181 (14 AP and 15 AC) dissecting aneurysms (18 of 29 occurred concurrently with marked residual irregularity and narrowing).

Of the 181 patients with confirmed dissection and complete imaging at baseline and 3 months, there was no difference in the presence of residual narrowing or occlusion between those receiving AP (n = 56 of 92) vs those receiving AC (n = 53 of 89) (P = .97).

The association of different clinical parameters with residual narrowing or occlusion are shown in **Table 4**. On univariate analyses, higher age, lower rates of migraine without aura, lower blood pressure, and higher rates of statin therapy were associated with residual narrowing/occlusion. On multivariate analysis, only age remained associated (**Table 5**). We also determined association of other imaging features of dissection with recanalization. On multivariate analysis, controlled for age and sex, only mural hematoma at baseline was positively associated with recanalization at 3 months (OR, 2.19; 95% CI, 1.16-4.20; P = .02).

Table 4. Baseline Characteristics, Angiographic Data

Characteristic	No. (%)					
	Narrowing and Occlusion at 3 mo			Recanalized at 3 mo		
	Yes (n = 109)	No (n = 72)	Univariate	Yes (n = 82)	No (n = 99)	Univariate
Age, mean (SD), y	50.2 (11.8)	45.3 (9.8)	0.003	45.1 (9.92)	50.9 (11.7)	0.0004
Male	70 (64.2)	55 (76.3)	0.08	61 (74.4)	64 (64.6)	0.21
Modified Rankin score, mean (SD)	2.26 (1.47)	1.86 (1.53)	0.08	1.95 (1.57)	2.23 (1.44)	0.22
Received stroke thrombolysis	13 (11.9)	3 (4.2)	0.13	4 (4.9)	12 (12.1)	0.15
Risk factors						
Diabetes mellitus	2 (1.8)	2 (2.8)		2 (2.4)	2 (2.02)	
Smoking history (ever smoked)	59 (54.1)	34 (47.2)	0.45	39 (47.6)	54 (54.5)	0.43
Migraine	20 (18.3)	15 (20.8)	0.82	16 (19.5)	19 (19.1)	0.89
History of trauma to head/neck within last 28 d	22 (20.2)	20 (27.8)	0.32	22 (26.8)	20 (20.2)	0.38
Blood pressure, mean (SD), mm Hg						
Systolic	135.2 (18.3)	137.9 (20.7)	0.37	138.5 (21.3)	134 (17.1)	0.15
Diastolic	80.9 (12.7)	86.8 (14.4)	0.01	86.3 (14.1)	80.7 (12.8)	0.007
Mean arterial pressure	99 (13.4)	103.8 (15.8)	0.04	103.7 (16.5)	98.6 (13.3)	0.02
Treated						
Hypertension	25 (22.9)	10 (13.9)	0.19	12 (14.6)	23 (23.2)	0.2
Hyperlipidemia	31 (28.4)	10 (13.9)	0.04	13 (15.9	28 (28.3)	0.07
Antiplatelets	56 (51.4)	36 (50)	0.97	41 (50)	51 (51.5)	0.96
Anticoagulants	53 (48.6)	36 (50)		41 (50)	48 (48.5)	

Table 5. Multivariate Analysis Showing Factors Associated With Recanalization on Follow-up Angiographic Imaging

Factor	OR (95% CI)	*P* Value
Clinical factors associated with recanalization		
Age	0.94 (0.91-0.97)	.001
Female	0.56 (0.27-1.15)	.12
ICA	1.9 (1.00-3.63)	.049
Thrombolysis	0.35 (0.09-1.13)	.10
Mean arterial pressure, 1 mm Hg	1.02 (0.99-1.05)	.08
Anticoagulation vs antiplatelets	1.04 (0.69-3.37)	.09
Imaging factors associated with recanalization		
Age	0.95 (0.92-0.98)	.002
Mural Hematoma	2.19 (1.16-4.20)	.02
Narrowing	1.08 (0.50-2.29)	.85
Occlusion	0.59 (0.28-1.26)	.17
Dissecting aneurysm	0.93 (0.33-2.70)	.89
Luminal flap/false lumen	0.78 (0.29-2.02)	.61
Anticoagulation vs antiplatelets	1.14 (0.60-2.15)	.68

Abbreviations: ICA, internal carotid artery; OR, odds ratio.

Adverse Events

Adverse events were collected during the first 3 months. There was 1 major bleed with AC in a patient with vertebral dissection with extension intracranially who developed a subarachnoid hemorrhage.

Discussion

In what is, to our knowledge, the first randomized study of AP vs AC therapy for extracranial carotid and vertebral dissection, we found a low rate of recurrent stroke and no difference between the 2 treatment arms. Although there were 4 strokes within 1 year of follow-up in the AP group and only 2 in the AC group, this was counterbalanced by 1 major hemorrhage in the AC group.

Results from the 1-year follow-up demonstrate that, in this population of prospectively recruited patients with complete follow-up, there was a low rate of recurrent stroke of 2.4% in the ITT population and 2.5% in the PP population up to 1 year. Of note, all recurrent events occurred in patients who had presented with stroke and none occurred in those presenting with only local symptoms. Our results demonstrate that not only was the early risk of stroke lower than that reported in some previous studies,[7,8] many of which were based on retrospective analysis with incomplete follow-up, but the later risk of recurrence between 3 and 12 months was also very low, with only 2 additional strokes in the 250 patients; of these, 1 was in each treatment arm. Our results are consistent with those from the nonrandomized arm of CADISS, which reported a similarly low rate: there were 2 recurrent strokes (2.3%) during the first 3 months of follow-up in 87 individuals with both carotid and vertebral dissection[2] and from a large retrospective analysis in 298 patients.[9] In a clinical trial setting, such as CADISS, it is possible that we may have missed some early recurrent strokes prior to recruitment; previous studies have suggested that recurrent strokes may be most frequent very early after initial stroke and TIA. A previous analysis of events prior to recruitment in the 3-month follow-up article[4] found that 7% of patients had such symptoms; this could mean that our estimates of recurrent stroke are underestimates by up to 7%, although many events were very close temporally to the presenting event and would be likely to have occurred prior to patient presentation.

Analysis of outcomes by treatment arm showed no difference between AP and AC therapy. However, the low number of end points means that a very large sample size, of many thousands, would be required to detect a treatment difference between the 2 therapies, but the low rate of events suggests that any absolute effect on outcome, even if, for example, there was a 25% reduction in risk, would be very low. Therefore, it seems reasonable to treat such patients with either AC or AP agents based on the available data.

Dissection is often accompanied by significant angiographic abnormalities including stenosis or occlusion and dissecting aneurysms. We also present the results of the imaging analysis from CADISS. There was no difference in the proportion of patients with residual occlusion and/or stenosis or with residual dissecting aneurysm between those treated with AP and AC. We also looked at factors associated with residual narrowing or stenosis; on multivariate analysis, increasing age was highly significantly associated with residual narrowing and occlusion. Of the angiographic markers, only occlusion at baseline was significantly associated with occlusion at 3 months. Therefore, analysis of the surrogate end point of recanalization also showed no evidence that either AC or AP was more effective.

The CADISS trial was designed as a pragmatic trial, and therefore the choice of AP agent was at the clinician's discretion. Approximately 55% were receiving a single AP, either clopidogrel or aspirin, and 45% received dual AP. Increasing evidence suggests that the combination of aspirin and clopidogrel may be more effective in preventing early recurrent stroke risk in patients with atherosclerotic large artery stenosis, and it is possible that AP may have been more effective if all patients had been given this combination. Patients receiving AC were all given warfarin because CADISS started before novel oral ACs, and therefore, we do not know how effective they are compared with AP in preventing stroke after dissection. However, data on stroke prevention in general suggests they are roughly equivalent in efficacy to warfarin.

Limitations

The CADISS trial is, to our knowledge, the first randomized clinical trial in the treatment of carotid and vertebral dissection that recruited the target and had complete follow-up of all patients to 1 year. Therefore, it provides the most robust data on which to guide therapy in this disease. However, it does have limitations. In approximately 20% of individuals, the diagnosis of dissection could not be confirmed radiographically. In some patients, imaging was not of sufficient quality to allow accurate review, but in other cases, diagnostic criteria were not rigorously applied and other causes of angiographic abnormalities were mistakenly diagnosed as dissection. This emphasizes the need for accurate neuroradiologic review to confirm the diagnosis. A further limitation is that clinical imaging was used to assess angiographic patency and different patients were imaged using CTA or MRA and on a variety of different scanner types.

Conclusions

In summary, CADISS showed a low risk of recurrent stroke up to 1 year in patients presenting with cervical dissection. It showed no difference in prevention of stroke, or of residual stenosis and occlusion, between patients treated with either AC or AP.

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