Aspirin versus anticoagulation in cervical artery dissection (TREAT-CAD): an open-label, randomised, non-inferiority trial

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Summary

Background Cervical artery dissection is a major cause of stroke in young people (aged <50 years). Historically, clinicians have preferred using oral anticoagulation with vitamin K antagonists for patients with cervical artery dissection, although some current guidelines—based on available evidence from mostly observational studies—suggest using aspirin. If proven to be non-inferior to vitamin K antagonists, aspirin might be preferable, due to its ease of use and lower cost. We aimed to test the non-inferiority of aspirin to vitamin K antagonists in patients with cervical artery dissection.

Methods We did a multicentre, randomised, open-label, non-inferiority trial in ten stroke centres across Switzerland, Germany, and Denmark. We randomly assigned (1:1) patients aged older than 18 years who had symptomatic, MRI-verified, cervical artery dissection within 2 weeks before enrolment, to receive either aspirin 300 mg once daily or a vitamin K antagonist (phenprocoumon, acenocoumarol, or warfarin; target international normalised ratio [INR] 2·0–3·0) for 90 days. Randomisation was computer-generated using an interactive web response system, with stratification according to participating site. Independent imaging core laboratory adjudicators were masked to treatment allocation, but investigators, patients, and clinical event adjudicators were aware of treatment allocation. The primary endpoint was a composite of clinical outcomes (stroke, major haemorrhage, or death) and MRI outcomes (new ischaemic or haemorrhagic brain lesions) in the per-protocol population, assessed at 14 days (clinical and MRI outcomes) and 90 days (clinical outcomes only) after commencing treatment. Non-inferiority of aspirin would be shown if the upper limit of the two-sided 95% CI of the absolute risk difference between groups was less than 12% (non-inferiority margin). This trial is registered with ClinicalTrials.gov, NCT02046460.

Findings Between Sept 11, 2013, and Dec 21, 2018, we enrolled 194 patients; 100 (52%) were assigned to the aspirin group and 94 (48%) were assigned to the vitamin K antagonist group. The per-protocol population included 173 patients; 91 (53%) in the aspirin group and 82 (47%) in the vitamin K antagonist group. The primary endpoint occurred in 21 (23%) of 91 patients in the aspirin group and in 12 (15%) of 82 patients in the vitamin K antagonist group (absolute difference 8% [95% CI −4 to 21], non-inferiority p=0·55). Thus, non-inferiority of aspirin was not shown. Seven patients (8%) in the aspirin group and none in the vitamin K antagonist group had ischaemic strokes. One patient (1%) in the vitamin K antagonist group and none in the aspirin group had major extracranial haemorrhage. There were no deaths. Subclinical MRI outcomes were recorded in 14 patients (15%) in the aspirin group and in 11 patients (13%) in the vitamin K antagonist group. There were 19 adverse events in the aspirin group, and 26 in the vitamin K antagonist group.

Interpretation Our findings did not show that aspirin was non-inferior to vitamin K antagonists in the treatment of cervical artery dissection.

Funding Swiss National Science Foundation, Swiss Heart Foundation, Stroke Funds Basel, University Hospital Basel, University of Basel, Academic Society Basel.

Introduction

Cervical artery dissection is one of the leading causes of stroke in young people (aged <50 years),[1] and the optimal type of antithrombotic treatment is unclear.[2] Historically, many clinicians have preferred using oral anticoagulation with vitamin K antagonists,[3] but this approach is not evidence-based,[4] and guidelines have either expressed no preference[5,6] or suggested using antiplatelets instead.[7] Findings of observational studies[8–13] and one randomised controlled trial, the cervical artery dissection in stroke study (CADISS)[14] comparing antiplatelets with vitamin K antagonists, have been inconclusive. Aspirin might be preferable because it is more convenient to use and less costly than vitamin K antagonists.[15] However, it remains to be shown

Lancet Neurol 2021

Published **Online** March 22, 2021 https://doi.org/10.1016/S1474-4422(21)00044-2

See **Online/Comment** https://doi.org/10.1016/S1474-4422(21)00073-9

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Research in context

Evidence before this study

We searched PubMed, Embase, the Cochrane library, and the ClinicalTrials.gov registry on Aug 27, 2020, with no language restrictions, to identify randomised controlled trials and meta-analyses comparing antiplatelets with anticoagulants in patients with cervical artery dissection, published between database inception and Aug 27, 2020. We used the search terms "dissection" AND "anticoagulants" AND "antiplatelets" AND ("carotid" OR "vertebral") on PubMed, the Cochrane Library, and ClinicalTrials.gov, and ("dissection"/exp OR "dissection") AND ("antithrombocytic agent"/exp OR "antithrombocytic agent") AND ("carotid artery"/exp OR "carotid artery" OR "vertebral artery"/exp OR "vertebral artery") on Embase. We identified six meta-analyses—including one Cochrane review—of observational data comparing antiplatelets with anticoagulants in patients with cervical artery dissection, which showed inconclusive results. There was one completed randomised controlled trial, the cervical artery dissection in stroke study (CADISS). The CADISS investigators found that recurrent strokes occurred in only four (2%) of 197 patients, which were numerically more frequent in the antiplatelet group (three [3%] of 101 patients) than in the anticoagulation group (one [1%] of 96), and the only major haemorrhage occurred in the anticoagulation group, but no clear difference between the antiplatelet and anticoagulant regimens was shown. Furthermore, the lower than expected clinical event rate in CADISS indicated that a randomised controlled trial based purely on clinical endpoints is not feasible. In one in five patients in the trial, the diagnosis of cervical artery dissection could not be confirmed by central imaging reading, suggesting that the correct diagnosis of cervical artery dissection is challenging in the acute phase. Historically, most clinicians have favoured using anticoagulants (mainly vitamin K antagonists) for patients with cervical artery dissection, but since the publication of the CADISS results, this practice has largely been abandoned, despite this change in practice not being well supported by the available evidence.

Added value of this study

Since previous evidence suggested that a randomised controlled trial in patients with cervical artery dissection comparing antiplatelets with anticoagulants that measured clinical endpoints only would not be feasible, our study implemented a novel approach with the use of a composite primary endpoint, comprising clinical outcomes (stroke, major haemorrhage, or death) and MRI outcomes (new ischaemic or haemorrhagic brain lesions). This approach enabled a reduction in the trial sample size to a feasible magnitude and allowed for the successful completion of the trial. The trial was designed to test the non-inferiority of aspirin to vitamin K antagonist treatment in patients with cervical artery dissection. Non-inferiority of aspirin was not shown. Furthermore, non-inferiority of aspirin was not shown when analysing clinical and MRI outcomes separately, nor across all sensitivity analyses.

Implications of all the available evidence

The evidence to consider aspirin as the standard of care in patients with cervical artery dissection is weak. Currently, it does not seem justified to replace the traditional standard treatment (anticoagulation) with aspirin, although the superiority of anticoagulation has also not been shown. The importance of the type of presenting symptom might be addressed in an individual patient data meta-analysis including CADISS and our trial. Direct oral anticoagulants have a more favourable benefit–risk ratio and are more conveniently applicable than are vitamin K antagonists. Thus, benefits and harms of direct oral anticoagulants in patients with cervical artery dissection should be tested in future trials.

whether aspirin is non-inferior to anticoagulants for cervical artery dissection, evidence for which is needed to support a preference for aspirin. Based on estimates derived from the aforementioned studies, a conventional trial testing this hypothesis is not feasible if based purely on clinical endpoints, because a large sample size would be required.[10,15] However, sufficient power in a randomised controlled trial could be achieved by combining both clinical and MRI outcomes. For this approach, the MRI substudy[16] of the International Carotid Stenting Study served as a role model, because the comparative analysis of MRI outcomes in both treatment groups (ie, stenting versus carotid endarterectomy) resulted in nearly identical results to those in the main study based on purely clinical outcomes, with less than 10% of the patients from the main study. More recently, the MRI substudies of the AVERROES[17] and the COMPASS[18] randomised trials found that clinical and MRI outcomes were concordant and thus their combined use has been advocated. In line with this recommendation, the REDUCE trial[19] implemented clinical and MRI outcomes as a co-primary outcome and showed the usefulness of this combination in a stroke-prevention randomised trial testing patent foramen ovale closure.

We aimed to test whether aspirin is non-inferior to vitamin K antagonists in the treatment of patients with cervical artery dissection, in terms of both safety and efficacy, using an approach with a composite clinical and MRI primary endpoint.

Methods

Study design

We did a randomised, open-label, multicentre, non-inferiority trial with blinded assessment of outcome events (the biomarkers and antithrombotic treatment in cervical artery dissection trial [TREAT-CAD] trial), in ten stroke centres across Switzerland, Germany, and Denmark

(appendix 1 pp 3–4). The trial design and rationale have been described previously.[20]

The trial was approved by the relevant ethics committees and regulatory authorities for each centre in Switzerland, Germany, and Denmark. Independent on-site and centralised monitoring was performed by the Clinical Trial Unit of the University Hospital Basel (Basel, Switzerland).

We followed the trial protocol (appendix 2 pp 1–28), and the trial was reported in accordance with the statistical analysis plan, which was finalised and published before database closure (Jan 14, 2020) and data analysis.

Participants

Potential trial participants were informed about TREAT-CAD and given the option to participate by local investigators, after patients had received their diagnosis from the treating doctor and been made aware of therapeutic options as part of the clinical routine. Patients aged older than 18 years, presenting at the participating centres with acute ischaemic (ie, transient ischaemic attack or ischaemic stroke) or non-ischaemic (ie, local signs) symptoms of cervical artery dissection within 2 weeks before enrolment were eligible to participate. Before enrolment, the clinical diagnosis of cervical artery dissection had to be confirmed by MRI techniques according to accepted diagnostic criteria (appendix 1 p 4).[1] For patients with preceding intravenous thrombolysis or endovascular treatment, enrolment was allowed only after a 24 h latency period.

Exclusion criteria were pregnancy, contraindications to MRI, and contraindications to use of aspirin or anticoagulation (vitamin K antagonists or heparin), as outlined in the corresponding summary of product characteristics in the countries of randomisation or according to the judgment of the treating doctor.[20] Written informed consent from the patient, next of kin, or an independent doctor (if applicable) was required before enrolment in the trial.

Randomisation and masking

Randomisation was computer-generated, using an interactive web response system, with stratification according to the participating sites. The randomisation sequence was generated by members of the Clinical Trial Unit of the University Hospital Basel (Basel, Switzerland). Participants were randomly assigned (1:1) to either aspirin or a vitamin K antagonist, with a simple randomisation algorithm, to reach an equal distribution within each centre. Independent imaging core laboratory adjudicators (Clinical Stroke & Imaging Analysis Lab Basel, University of Basel, Basel, Switzerland; appendix 1 p 2) were masked to the allocated treatment, but investigators, patients, and the independent clinical event adjudication committee members (appendix 1 p 2) were aware of treatment allocation. Study investigators (appendix 1 pp 3–4) recruited and randomised the participants, and accordingly assigned participants to their respective treatment. These investigators also performed the follow-up visits.

Procedures

In the aspirin group, patients received oral aspirin 300 mg once daily. In individuals with dysphagia, intravenous aspirin 250 mg once daily was allowed instead, until swallowing function had recovered. In the vitamin K antagonist group, patients received phenprocoumon, acenocoumarol, or warfarin according to local practices and commercial availability of the medications in the respective centres and countries, with a target international normalised ratio (INR) of 2·0–3·0. Bridging treatment with intravenous heparin or low-molecular-weight heparin was recommended until the target INR had been reached. INR monitoring during the study treatment period was at the discretion of the treating doctor, according to common practice in each centre. The use of low-dose prophylactic heparin for prevention of deep-vein thrombosis was allowed in the aspirin group. Treatment duration in both groups within the trial was 90 days or until occurrence of the primary endpoint. There were no predefined rules for treatment discontinuation or dose reduction; this was done at the discretion of the treating physician if deemed clinically necessary.

At 14 days (plus or minus 10 days) after commencing treatment, participants had their first follow-up visit, with clinical and MRI (3 Tesla) assessments including the following MRI sequences: diffusion-weighted imaging including apparent diffusion coefficient maps to detect new acute ischaemic brain lesions; paramagnetic sequences (ie, T2*-weighted gradient echo or susceptibility-weighted images) to detect new haemorrhagic brain lesions; and contrast-enhanced magnetic resonance angiography with fat suppression to improve delineation of the wall haematoma against the perfused vessel lumen. At 90 days (plus or minus 30 days), patients had their second follow-up visit, with clinical assessment only. The pre-scheduled follow-up visits were also done for participants in whom primary endpoints had occurred before the scheduled visits or in whom major protocol violations had occurred.

Outcomes

The primary endpoint was a composite of clinical outcomes (ischaemic stroke, major extracranial or intracranial haemorrhage, or death) and MRI outcomes (new ischaemic or haemorrhagic brain lesions), which were defined by applying established criteria (appendix 1 pp 4–5).[21–23]

Clinical components of the primary endpoint were independently adjudicated by members of the clinical event adjudication committee, who were aware of treatment allocations. The MRI components of the primary endpoint were centrally adjudicated by independent imaging core laboratory adjudicators, who were unaware of treatment allocations and clinical outcomes of participants. Confirmation of the cervical artery dissection diagnosis was done centrally in a consensus reading by two experienced investigators (STE and CT). Secondary endpoints included (alongside all components of the

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See **Online** for appendix 1

See **Online** for appendix 2

For the **statistical analysis plan** see https://clinicaltrials.gov/ct2/show/NCT02046460

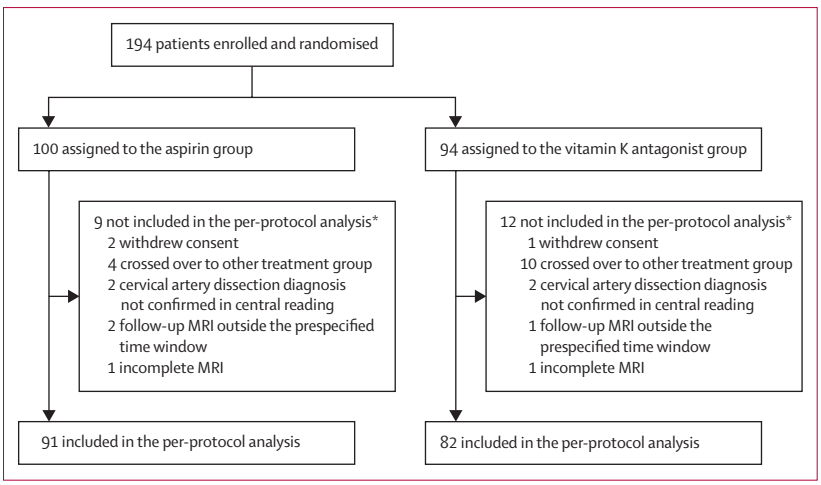

Figure 1: **Trial profile**
*Four patients (two in each group) met more than one of these criteria.

composite primary endpoint analysed separately): any increase (from baseline) in volume of the vessel wall haematoma (as detected in the follow-up cervical MRI); functional outcome at 3 months, as assessed with the modified Rankin Scale score; any transient ischaemic attack according to a clinical definition (ie, new neurological symptoms or deficits lasting less than 24 h with no new infarction on neuroimaging);[21] and recurrent cervical artery dissection during the follow-up period. Safety was monitored by the recording of adverse events and serious adverse events. As specified within the trial data safety monitoring board charter, the board assessed patient safety after enrolment of 80% of the original target sample size. The data safety monitoring board (appendix 1 p 2) concluded that there were no safety issues at that time and that enrolment could be completed as planned.

Statistical analysis

The sample size for the trial was calculated to be able to show the non-inferiority of aspirin to vitamin K antagonists in patients with cervical artery dissection with regard to the primary endpoint in the per-protocol population (appendix 1 pp 5–6). We expected a primary endpoint rate of 7% in both treatment groups (2% clinical outcomes[8,10,11] and 5% subclinical MRI outcomes[23]). Thus, 169 evaluable participants for per-protocol population analysis were required to ensure at least 80% power ($1–\beta=0\cdot8$) at a significance level of $\alpha=5\%$ (two-sided). To ensure that we would achieve the required number of 169 patients in the per-protocol population, we did a pre-planned (protocol version 3.1, dated June 27, 2016), blinded, interim analysis after recruitment of 80% (n=136) of the initial target sample size. We did not analyse treatment allocations or the occurrence of primary outcomes. Instead, we inspected the number of patients with major protocol deviations, who would not meet the criteria for per-protocol analysis. 18 (13%) of 136 recruited patients had major protocol violations. By extrapolating this rate, we estimated that a total of 194 participants had to be recruited to have data from at least 169 evaluable patients in the per-protocol population.

Continuous data are presented as mean (SD) or median (IQR) as appropriate. For categorical variables, absolute and relative frequencies are presented. To address the main objective, the absolute risk difference between patients in the aspirin group and patients in the vitamin K antagonist group is presented with 95% CI using Wilson's method (continuity-corrected modification of Wilson's score method). In addition, a test for the null hypothesis (absolute risk difference ≥12%) was estimated using the Z_{cu} statistics as suggested by Kawasaki and colleagues.[24] Non-inferiority would be declared if the upper limit of the two-sided 95% CI of the absolute risk difference was less than 12% (the non-inferiority margin). Due to the absence of unbiased information about treatment effects when the trial was designed, the non-inferiority margin could not be based on statistically guided estimates. Thus, the margin reflected the absolute difference of events, for which clinicians might still accept non-inferiority between both treatment groups, although this decision is debatable. This rather large margin was defined on the basis that the primary endpoint included clinical outcomes as well as subclinical MRI outcomes.

The main analysis was done on the per-protocol population dataset, which comprised patients who received the allocated treatment and completed the assessment period. For sensitivity analyses, the primary analysis was repeated: on the full analysis dataset with worst-case and best-case imputations for missing outcome data (intention-to-treat principle) and inverse probability weighting, to assess the effect of patients excluded from the per-protocol population; using clinical outcomes only; and using MRI outcomes only. No multiplicity adjustments were made. We did the following post-hoc sensitivity analyses: first, to evaluate whether crossovers to the other treatment group had any effect on our key finding, we did a post-hoc analysis in the as-treated population. This analysis included all patients in the per-protocol population plus those who had been excluded from the per-protocol population because they had not received the medication they were assigned to but that of the other treatment group instead. Second, as the meaning of new subclinical haemorrhagic brain lesions as seen on paramagnetic (ie, susceptibility-weighted imaging or gradient echo) MRI sequences is not well established, we did a post-hoc sensitivity analysis excluding these lesions from the primary outcome. Third, as the rate of acute recanalisation procedures might be a confounder, we did an additional post-hoc sensitivity analysis on the primary outcome excluding all patients who had an acute recanalisation procedure before enrolment in the trial. Analyses were done using the statistical software package R, version 3.6.3.

This trial is registered with ClinicalTrials.gov, NCT02046460.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Sept 11, 2013, and Dec 21, 2018, we enrolled 194 patients (figure 1); 100 (52%) were randomly assigned to the aspirin group and 94 (48%) to the vitamin K antagonist group (78 received phenprocoumon, 12 acenocoumarol, and four warfarin). 51 (54%) of 94 patients received heparin or low-molecular-weight heparin followed by a vitamin K antagonist, whereas 43 patients (46%) received a vitamin K antagonist only. Mean duration of follow-up was 90·8 days (range 83–104) in the aspirin group and 90·5 days (range 87–104) in the vitamin K antagonist group.

21 (11%) of 194 patients did not meet criteria for per-protocol analysis (figure 1), including 14 patients who crossed over to the other treatment group. Although all patients had brain and cervical MRI scans at baseline, these were incomplete in one patient in the aspirin group and one in the vitamin K antagonist group. Therefore, the per-protocol population consisted of 173 patients (89% of study participants), of whom 91 (53%) received aspirin and 82 (47%) received a vitamin K antagonist. Among the per-protocol population, cervical artery dissection involved the carotid artery in 115 (66%) patients and the vertebral artery in 61 (35%) patients, including three (2%) with involvement of the carotid artery plus the vertebral artery. Mural haematoma was the most frequent imaging characteristic identified on baseline MRI (in 165 patients [95%]; table 1).

23 (13%) of 173 patients in the per-protocol population and 23 (26%) of 90 patients presenting with stroke had acute revascularisation procedures before enrolment. In these patients, enrolment was allowed only after a 24-h interval as specified in the inclusion criteria. Study treatment was commenced a median of 3 days after hospital admission, and this did not differ between treatment groups. Detailed history-taking revealed that the first symptom of cervical artery dissection, which was pain in most patients, had occurred a median of 7 days before starting study treatment.

The primary endpoint occurred in 33 (19%) of 173 patients in the per-protocol population; 21 (23%) of 91 patients in the aspirin group versus 12 (15%) of 82 patients in the vitamin K antagonist group (table 2). Of these 33 patients, 32 (97%) presented with either clinical ischaemic events, MRI lesions, or both at baseline. The observed absolute difference in the primary endpoint rate between groups was 8% (95% CI –4 to 21; non-inferiority p=0·55; figure 2; appendix 1 pp 6–7). In sensitivity analyses, point estimates and 95% CIs of the event rates for the full analysis set population, those with MRI outcomes only, and those with clinical outcomes only in the per-protocol population closely resembled those of the

	Per-protocol population (n=173)		Full analysis set population (n=194)	
	Aspirin group (n=91)	Vitamin K antagonist group (n=82)	Aspirin group (n=100)	Vitamin K antagonist group (n=94)
Age, years	46·7 (10·2)	45·5 (11·6)	46·6 (10·6)	45·5 (11·6)
Sex				
Male	56 (62%)	54 (66%)	62 (62%)	61 (65%)
Female	35 (38%)	28 (34%)	38 (38%)	33 (35%)
Site of dissection				
Internal carotid artery	65 (71%)	50 (61%)	72 (72%)	58 (62%)
Vertebral artery	27 (30%)	34 (41%)	29 (29%)	38 (40%)
Multivessel dissection	8 (9%)	5 (6%)	9 (9%)	5 (5%)
Occlusion of dissected artery	32 (36%)*	23 (28%)	35 (35%)*	26 (28%)
Mural haematoma of dissected artery	89 (98%)	76 (93%)	97 (97%)	88 (94%)
Presenting signs and symptoms				
Presenting cerebral ischaemic events†				
Ischaemic stroke	47 (52%)	43 (52%)	52 (52%)	49 (52%)
Transient ischaemic attack	12 (13%)	10 (12%)	14 (14%)	10 (11%)
Retinal infarct	3 (3%)	1 (1%)	3 (3%)	1 (1%)
Amaurosis fugax	2 (2%)	5 (6%)	2 (2%)	7 (7%)
Presenting local signs				
Cervical pain	46 (51%)	41 (50%)	51 (51%)	47 (50%)
Headache	65 (71%)	54 (66%)	72 (72%)	64 (68%)
Cranial nerve palsy	11 (12%)	7 (9%)	11 (11%)	7 (7%)
Horner's syndrome	32 (35%)	28 (34%)	36 (36%)	34 (36%)
Tinnitus	13 (14%)	4 (5%)	13 (13%)	6 (6%)
Modified Rankin Scale score‡	1·8 (1·2)	1·8 (1·3)	1·8 (1·2)	1·8 (1·3)
NIHSS score‡	2·1 (2·9)	2·5 (4·3)	2·1 (2·7)	2·5 (4·1)
Time between hospital admission and treatment, days	2·8 (1·2–4·9)	3·0 (1·5–5·4)	2·9 (1·3–4·8)	3·0 (1·5–5·4)
Time between onset of first cervical artery dissection symptom and treatment, days	7·0 (4·0–10·0)	6·0 (3·2–8·8)	7·0 (4·0–10·0)	6·0 (4·0–9·0)
Acute recanalisation therapy				
Intravenous thrombolysis	12 (13%)	7 (9%)	13 (13%)	9 (10%)
Endovascular therapy or bridging	3 (3%)	1 (1%)	3 (3%)	2 (2%)
Risk factors				
Hypertension	30 (33%)	25 (30%)	32 (32%)	28 (30%)
Hypercholesterolaemia	18 (20%)	18 (22%)	19 (19%)	20 (21%)
Diabetes	1 (1%)	3 (4%)	1 (1%)	3 (3%)
History of smoking	43 (47%)	42 (51%)	46 (46%)	47 (50%)
Migraine with aura	13 (14%)	10 (12%)	13 (13%)	11 (12%)
Migraine without aura	17 (19%)	7 (9%)	18 (18%)	8 (9%)
Mechanical trigger event within 4 weeks before enrolment	12 (13%)	16 (20%)	13 (13%)	18 (19%)
Infection within 4 weeks before enrolment	24 (26%)	15 (18%)	27 (27%)	18 (19%)
Baseline MRI characteristics				
Acute ischaemic lesion	47 (52%)	47 (57%)	51 (52%)§	51 (55%)§
Haemorrhagic lesion	7 (8%)	5 (6%)	7 (7%)	6 (6%)
Verification of dissection in central MRI reading	91 (100%)	82 (100%)	98 (98%)	92 (98%)

Data are n (%), mean (SD), or median (IQR). NIHSS=National Institutes of Health Stroke Scale. *Data missing for one patient. †11 patients had multiple ischaemic events. ‡In patients with ischaemic stroke. §Baseline MRI incomplete in one patient.

Table 1: **Baseline characteristics**

main analysis (figure 2). In the full analysis set population there was one additional MRI outcome (ischaemic lesion) in a patient in the aspirin group. In this patient, diagnosis of cervical artery dissection was not confirmed in central MRI reading. No further outcomes were detected in either group. In four of 194 patients in the full analysis set population, information on presence or absence of primary endpoints was missing and these missing data were imputed.

	Per-protocol population (n=173)		Full analysis set population (n=194)	
	Aspirin group (n=91)	Vitamin K antagonist group (n=82)	Aspirin group (n=100)*	Vitamin K antagonist group (n=94)†
Primary endpoint				
Composite of clinical outcomes and MRI outcomes	21 (23%)	12 (15%)	22 (23%)	12 (13%)
Clinical outcomes	7 (8%)	1 (1%)	7 (7%)	1 (1%)
Ischaemic stroke	7 (8%)‡	0	7 (7%)‡	0
Major extracranial haemorrhage	0	1 (1%)	0	1 (1%)
Symptomatic intracranial haemorrhage	0	0	0	0
Death	0	0	0	0
MRI outcomes (all)	20 (22%)	11 (13%)	21 (22%)	11 (12%)
New acute ischaemic brain lesion	9 (10%)	6 (7%)	10 (10%)	6 (6%)
New haemorrhagic brain lesion	9 (10%)	4 (5%)	9 (9%)	4 (4%)
New acute ischaemic and haemorrhagic lesion	2 (2%)	1 (1%)	2 (2%)	1 (1%)
MRI outcomes without symptoms	14 (15%)	11 (13%)	15 (15%)	11 (12%)
New acute ischaemic brain lesion	3 (3%)	6 (7%)	4 (4%)	6 (6%)
New haemorrhagic brain lesion	9 (10%)	4 (5%)	9 (9%)	4 (4%)
New acute ischaemic and new haemorrhagic lesion	2 (2%)	1 (1%)	2 (2%)	1 (1%)
Secondary endpoints				
Recurrent dissection	3 (3%)	2 (2%)	3 (3%)§	2 (2%)¶
Increase of vessel wall haematoma	1 (1%)	1 (1%)	1 (1%)§	5 (5%)¶
Transient ischaemic attack	0	2 (2%)	0§	2 (2%)¶
Excellent functional outcome (mRS score 0–1 at 3 months)	70 (77%)	62 (77%)¶	78 (79%)¶	72 (78%)‖
Independence in activities of daily living (mRS score 0–2 at 3 months)	88 (97%)	80 (99%)¶	96 (97%)¶	90 (98%)‖

Data are n (%). mRS=modified Rankin Scale. *Data on primary endpoint available for 97 patients. †Data on primary endpoints available for 93 patients. ‡Including one patient with retinal infarction. §Incomplete follow-up data for three patients. ¶Incomplete follow-up data for one patient. ‖Incomplete follow-up data for two patients.

Table 2: **Primary and secondary endpoints**

During follow-up, ischaemic stroke occurred in seven (8%) of 91 patients in the aspirin group (six brain infarcts and one retinal infarct, all ipsilateral to the cervical artery dissection at baseline) and did not occur in the vitamin K antagonist group. These events occurred either on day 1 (n=5) or day 7 (n=2). Five of these seven patients in the aspirin group had ischaemic strokes (or a retinal infarct) as a presenting symptom, with a mean National Institutes of Health Stroke Scale score of 1·6 points (range 0–4). Ischaemic lesions on baseline MRI were present in five of these seven patients. Major haemorrhage occurred in one (1%) of 82 patients in the vitamin K antagonist group (upper gastrointestinal bleed on day 7) and did not occur in the aspirin group. There were no deaths during the follow-up period.

Primary endpoints from MRI outcomes were recorded in 20 (22%) of 91 patients in the aspirin group and in 11 (13%) of 82 patients in the vitamin K antagonist group (table 2). MRI outcomes were associated with clinical symptoms in six (30%) of 20 patients in the aspirin group, but in none of the 11 patients in the vitamin K antagonist group .

There were 19 adverse events in the aspirin group, one of which was a serious adverse event, and 26 adverse events in the vitamin K antagonist group, six of which were serious adverse events (table 3). All seven patients with serious adverse events recovered completely. In the aspirin group, adverse events led to discontinuation (n=1) or dose reduction (n=1) of the allocated treatment in two patients. In the vitamin K antagonist group, adverse events led to treatment crossover to aspirin in three patients.

In a post-hoc sensitivity analysis in the as-treated population, patients who crossed treatment groups were

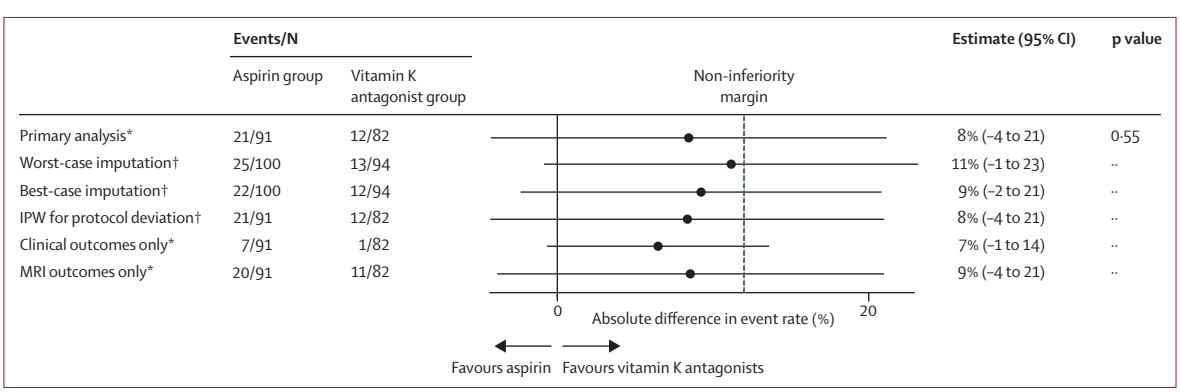

Figure 2: **Forest plot of the primary analysis and sensitivity analyses**
Results are given as absolute risk differences (black points) with 95% CI (black line) for the primary endpoint (ie, the composite of clinical outcomes [stroke, major haemorrhage, death] and MRI outcomes [new ischaemic or haemorrhagic brain lesions]). Non-inferiority of aspirin would be shown if the upper limit of the 95% CI of the absolute risk difference between groups was less than 12% (non-inferiority margin, indicated by the grey dashed line). IPW=inverse probability weighting. *Analyses were done on the per-protocol population dataset. †Analyses were done on the full analysis set population.

included (nine crossovers from vitamin K antagonist to aspirin and two crossovers from aspirin to vitamin K antagonist). Another three patients who crossed treatment groups were not included because their diagnosis of dissection had not been confirmed by central MRI reading (n=2) or because the other treatment had eventually not been started (n=1). In this as-treated population, the observed difference of the primary endpoint rate between groups was 7% (95% CI –5 to 19), which was consistent with the primary analysis. In another post-hoc sensitivity analysis excluding new subclinical haemorrhagic brain lesions, the observed difference between groups was 3% (95% CI –7 to 14).

Among the 23 patients who had acute revascularisation procedures before study participation, none had a clinical outcome event. However, seven patients had subclinical MRI lesions; five (33%) of 15 patients in the aspirin group and two (25%) of eight patients in the vitamin K antagonist group who had revascularisation procedures before enrolment. In the post-hoc sensitivity analysis excluding all patients who had acute recanalisation procedures before enrolment, the observed difference of the primary endpoint rate between groups was 5% (95% CI –8 to 18).

Discussion

In this multicentre, randomised controlled trial comparing aspirin with vitamin K antagonists in the treatment of cervical artery dissection, using a composite endpoint of clinical and MRI outcomes, non-inferiority of aspirin was not established. Ischaemic stroke, major haemorrhage, or their MRI surrogates occurred in approximately one in four patients in the aspirin group (23%), but in only one in seven patients in the vitamin K antagonist group (15%). As the upper limit of the 95% CI of the resulting 8% absolute difference in primary endpoint rates between groups (ie, 21%) exceeded the predefined margin of 12%, non-inferiority of aspirin compared with vitamin K antagonists was not shown.

The primary analysis finding was confirmed in sensitivity analyses across all study patients. Thus, the predefined methodological decision to base the main analysis on the per-protocol population had no effect on the key findings of the trial. Moreover, analyses of differences between groups in clinical outcomes only or MRI outcomes only had the same results as the main analyses using the composite endpoint. Therefore, if we had restricted the study to clinical outcomes only, aspirin would still not have been shown to be non-inferior to vitamin K antagonists. The concordance across all components of the composite primary endpoint and across all sensitivity analyses are evidence against the randomness of our key finding.

Among the primary endpoints, both clinical outcomes and MRI outcomes occurred numerically more often in the aspirin group than in the vitamin K antagonist group. For clinical outcomes, five of six meta-analyses of observational studies have suggested that ischaemic strokes could be expected in similar frequency in both treatment groups,[8–12] whereas one meta-analysis reported a higher rate of ischaemic strokes among patients treated with antiplatelets (6·9%) than in patients treated with anticoagulants (2·3%).[13]

In our trial, all seven ischaemic strokes occurred in the aspirin group, and the only major haemorrhage occurred

	Aspirin group (n=100)	Vitamin K antagonist group (n=94)
Total adverse events	19	26
Implantation of a knee endoprosthesis	1 (1%)	0
Hypertension	0	2 (2%)
Syncope	0	2 (2%)
Nausea	0	1 (1%)
Gastroenteritis	1 (1%)	0
Sore throat	0	1 (1%)
Stomach pain	0	1 (1%)
Xerostomia	1 (1%)	0
Cough	1 (1%)	0
Viral infection	1 (1%)	0
Renal cystic tumour, incidental finding	1 (1%)	0
Exercise-induced dyspnoea	1 (1%)	0
Depressive episode	1 (1%)	0
Tachycardia	1 (1%)	0
Suspicion of PEG-tube infection	1 (1%)	0
Obstructive sleep apnoea syndrome	0	1 (1%)
Epistaxis	1 (1%)	1 (1%)
Constipation associated with opioid intake	1 (1%)	0
Alopecia	0	2 (2%)
Worsening of headache	3 (3%)	0
Worsening of cervical pain	0	1 (1%)
Accident induced haematoma on knee joint	0	1 (1%)
Subconjunctival eye haemorrhage	0	1 (1%)
Fall-induced occipital laceration wound	0	1 (1%)
Nephrolithiasis	0	1 (1%)
Dizziness	0	2 (2%)*
Herpes zoster	1 (1%)	0
Benign paroxysmal positional vertigo	0	1 (1%)
Panic attacks	1 (1%)	0
Atrial fibrillation	1 (1%)	0
Exanthema, possibly drug related	0	1 (1%)
Loss of libido	0	1 (1%)
Seizure	1 (1%)†	2 (2%)†
Migraine equivalent	0	1 (1%)†
Allergic reaction to MRI contrast agent	0	1 (1%)†
Hospitalisation due to suspected recurrent stroke	0	1 (1%)†

Data are n or n (%). Wording of adverse events as provided by centre. PEG=percutaneous endoscopic gastrostomy. *One case was a serious adverse event. †Serious adverse events.

Table 3: **Adverse events**

in the anticoagulation group. Similarly, in the CADISS trial,[14] ischaemic strokes also occurred numerically more often in the antiplatelet group (three [2%] of 124 patients) than in the vitamin K antagonist group (one [1%] of 126 patients) and the only major haemorrhage also occurred in the vitamin K antagonist group. A simple study-level meta-analysis across clinical outcomes (stroke, major haemorrhage, death) in both the CADISS trial and our trial showed no significant difference in outcome rates between treatment groups (aspirin group 5% *vs* vitamin K antagonist group 2%, absolute difference 3% [95% CI –1 to 8], p=0·12). The reasons for the higher rate of ischaemic strokes in the aspirin group in our trial compared with the antiplatelet group in the CADISS trial remain unknown. Comparing the baseline characteristics of patients in the antiplatelet groups in both trials, there were no signs that the aspirin group in our trial was comprised of patients with an especially high risk for subsequent stroke. In the CADISS trial, a quarter of patients in the antiplatelet group received aspirin plus clopidogrel. In our trial, all patients received aspirin as monotherapy, albeit in a higher daily dose of 300 mg. Whether this variation could convincingly explain the difference in clinical event rates remains unclear.

In patients with cervical artery dissection, most strokes reportedly occur soon after the initial symptoms.[25] However, in our trial, time from symptom onset to start of treatment did not differ between treatment groups and is therefore not a plausible reason for the higher stroke rate in the aspirin group. Previous research showed that occlusion of the dissected artery, multivessel dissection, and vertebral artery as the site of dissection might increase the risk of delayed stroke (ie, stroke after hospital admission) in patients with cervical artery dissection.[26] Significant differences in baseline characteristics between groups were absent. However, occlusion of the dissected artery and multivessel dissections were numerically more frequent in the aspirin group than in the vitamin K antagonist group (32 [36%] of 90 patients *vs* 23 [28%] of 82 patients and eight [9%] of 91 patients *vs* five [6%] of 82 patients respectively). On the other hand, the vertebral artery as the site of dissection was more common in the vitamin K antagonist group (42%) than in the aspirin group (30%). Likewise, acute ischaemic lesions present at baseline imaging as a determinant for recurrent lesions[23] were numerically more frequent in the vitamin K antagonist group (57%) than in the aspirin group (52%). Moreover, ischaemic stroke as the presenting symptom, which is a known strong predictor for recurrent stroke in patients with cervical artery dissection, was present as often in the aspirin group (52%) as in the vitamin K antagonist group (52%). Thus, the observed between-group differences in event rates should not be attributable to differences in baseline characteristics.

Patients in the vitamin K antagonist group who had received the recommended bridging with heparin or low-molecular-weight heparin in addition to a vitamin K antagonist before reaching the target INR might have had better protection against early ischaemic strokes (particularly on day 1) than patients treated with aspirin, which could be a possible explanation for the observed higher rate of ischaemic strokes in the aspirin group than in the anticoagulation group.

As with the clinical outcome of ischaemic strokes, numerically more subclinical ischaemic MRI lesions occurred in the aspirin group (n=11) than in the vitamin K antagonist group (n=7). This imbalance is contrasted by previous non-randomised observations that the type of antithrombotic treatment had no effect on the occurrence of new ischaemic lesions in the observational cohort (odds ratio 1·0, 95% CI 0·32–3·15).[23]

Unexpectedly, numerically more haemorrhagic MRI lesions occurred in the aspirin group (n=11) than in the anticoagulation group (n=5). However, the interpretation of the pathophysiological meaning of small lesions on paramagnetic MRI might be more complex, as some of these lesions might reflect haemorrhagic transformation,[27] which also occurs in the context of non-cervical-artery-dissection ischaemic strokes[28] and can be accompanied by ischaemic brain lesions, as was the case in some of the patients in our trial.

With one exception, all primary endpoints (clinical outcomes or MRI outcomes) occurred in patients who had either ischaemic events or MRI lesions at baseline, underlining the prognostic importance of these characteristics, as suggested by previous research.[14,26] However, this trial was not powered for conclusive analyses in subgroups.

MRI outcomes occurred more often than did clinical outcome events (approximately four times as frequently), which was in line with our assumptions when designing the trial. Importantly, the consistent findings across both clinical outcomes and MRI outcomes strengthen the conclusion of the trial. The clinical meaning of MRI outcomes without accompanying clinical symptoms is debated and indeed unclear.[29] Although some studies have suggested that MRI outcomes might be useful as surrogates for clinical outcomes,[17,18,30] MRI outcomes cannot entirely replace clinical endpoints. Nevertheless, it is possible that MRI outcomes are associated with the occurrence of psychosocial sequelae, which have been reported at a high rate in otherwise well recovered patients with cervical artery dissection.[31] Since patients with cervical artery dissection are often young (aged 30–50 years) with no relevant comorbidities,[1] we assume that the occurrence of new ischaemic or haemorrhagic brain lesions is a disadvantage, whether they are reflected as clinical signs in neurological examinations or not.

An important limitation of our trial is the large non-inferiority margin that, due to the absence of reliable data at the time of study design, was not guided by calculated estimates but reflected the limit for non-inferiority between both treatment groups as chosen when TREAT-CAD was designed. This decision is debatable: the larger the margin the more likely that a higher number of events

in the aspirin group would still be considered non-inferior. Thus, the large margin would have been a more important limitation had we shown non-inferiority of aspirin than it is for our results that did not show non-inferiority despite a large margin.

A further limitation is the large 95% CI for the primary endpoint, which shows the poor precision for the observed difference in the treatment effect between treatment groups, meaning a cautious interpretation of the point estimate is required. In addition, the use of a composite primary outcome, although used in a previous randomised trial,[19] does not support the idea that all components are equally important and that they have the same treatment response.

The numerically higher frequency of acute recanalisation procedures in the aspirin group might be a confounder, as acute recanalisation procedures involve the risk of clinical or subclinical MRI outcomes as a complication. We tried to minimise the influence of these procedures by requiring a 24-h delay before enrolment was allowed. However, periprocedural, clinical, or subclinical outcomes that occurred after the 24-h interval could have interfered.

A major limitation of the non-inferiority design is that this trial could not show that aspirin is worse than or inferior to vitamin K antagonists in the treatment of cervical artery dissection, as the study was not designed or powered to address the question of superiority of either treatment. It is important to emphasise that although aspirin was not shown to be non-inferior to vitamin K antagonists, these results do not mean that aspirin is worse than anticoagulants or that vitamin K antagonists are superior to aspirin. Moreover, as most study participants presented with minor-to-moderate strokes, transient ischaemic attacks, or non-ischaemic symptoms, the applicability of our key findings to patients with major or disabling stroke is not clear.

A strength of our trial was that centres had a special interest in the diagnosis and treatment of cervical artery dissection. Their expertise translated into a rate of verified dissections of greater than 97%, negating the issue that correct diagnosis of cervical artery dissection in acute settings is challenging.[15] Independent and central adjudication of both clinical outcomes and imaging outcomes helped to support the validity of the results. Analyses of clinical outcomes and MRI outcomes were concordant, which is evidence against these results being spurious findings.

We did not use dual antiplatelet therapy in our trial because this acute stroke treatment regimen was not well established when the study was designed. Given the results of the CHANCE trial[32] and the POINT trial,[33] the use of dual antiplatelets might be considered in future trials, as this has not been specifically tested in the CADISS trial nor TREAT-CAD. Likewise, a treatment duration of less than 3 months could be tested, given the early occurrence of ischaemic events observed in this trial.

For regulatory reasons, we were unable to include direct oral anticoagulants in the anticoagulation group (the ethics committee did not allow them to be included due to scarcity of data at the time of the study). In small case-series, direct oral anticoagulants have been used in patients with cervical artery dissection.[34–37] In general, direct oral anticoagulants have a more favourable risk–benefit ratio and are more conveniently applicable than are vitamin K antagonists. However, it is unclear whether these advantages apply for the treatment of cervical artery dissection. Thus, benefits and harms of direct oral anticoagulants versus vitamin K antagonists in cervical artery dissection should be compared in future trials.

Contributors

STE, CT, MA, and PL contributed to study design, selection of participating centres, acquisition of the funding, grant, and ethical approval, protocol development, data collection and interpretation, and writing of the manuscript. STE and CT accessed and verified all underlying data. HG and LHB contributed to study design, acquisition of funding, protocol development, data collection and interpretation, and critical review of the manuscript. SAS contributed to study design, statistical analysis, data interpretation, and drafting of the manuscript. NB contributed to study design, trial operations, site monitoring, data management, and critical review of the manuscript. ARL, PM, GK, KN, TK, LK, SR, RS, CHN, HC, SW, and CS contributed to study design, protocol development, data collection and interpretation, and critical review of the manuscript. BGS, SLL, SJ, JG, UF, DS, KF, AAP, LS, JH, GMDM, NP, GS, JV, and RvR contributed to data collection, data interpretation, and critical review of the manuscript. AB and M-NP contributed to imaging core lab adjudication, data interpretation, and critical review of the manuscript. All authors read and approved the final manuscript. All authors vouch for the completeness and accuracy of the data and analyses, for the reporting of the trial results as well as adverse events, and for the adherence of the trial conduct to the protocol. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

STE reports grants from Swiss National Science Foundation, Swiss Heart Foundation, Freiwillige Akademische Gesellschaft Basel, University of Basel, and University Hospital Basel, during the conduct of the study. CT reports grants from Swiss Heart Foundation, University of Basel, Bangerter-Rhyner Foundation, and Freiwillige Akademische Gesellschaft Basel; and travel honoraria from Bayer, outside of the submitted work. MA reports grants from Swiss National Science Foundation and Swiss Heart Foundation, during the conduct of the study; personal fees from Bayer, Bristol Myers Squibb, Covidien, Medtronic, Amgen, Daiichi Sankyo, Nestle Health Science, and Boehringer Ingelheim, outside of the submitted work. LHB reports grants from Swiss National Science Foundation, during the conduct of the study; and grants from Swiss Heart Foundation and University of Basel; grants and non-financial support from AstraZeneca; personal fees from Amgen, Bristol Myers Squibb, and Claret Medical; and personal fees and non-financial support from Bayer, outside of the submitted work. UF reports grants from Medtronic and consultancy to Medtronic, Stryker, and CSL Behring, outside of the submitted work. HG reports advisory board honoraria from Daiichi Sankyo and funding for travel from Bristol Myers Squibb and Pfizer, outside of the submitted work. BGS reports grants from Swiss National Science Foundation, during the conduct of the study. JG reports grants from Medtronic, outside of the submitted work. JH reports personal fees from Pfizer, outside of the submitted work. LK reports funding for travel or speaker honoraria from Bayer Vital, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, and Pfizer, outside of the submitted work. ARL reports personal fees from Amgen and Bayer, outside of the submitted work. PL reports grants from Bayer, Swiss National Science Foundation, and ProPatient Foundation of the University Hospital Basel; travel grants from Bayer and Pfizer; advisory board compensation from Bayer, Pfizer, Daiichi Sankyo, Bristol Myers Squibb, Recordati, and Amgen; and compensation for research activities from Sanofi and Acticor, outside of the submitted work. PM reports grants from University Hospital Basel for and during the conduct of the study; grants from Swiss National Science Foundation, Swiss Heart Foundation, ERISTA (Bristol

Myers Squibb and Pfizer) programme; and personal fees from Medtronic all used for education and research, outside of the submitted work. CHN reports patient fee compensation from University Hospital Basel, during the conduct of the study; and payments for lectures from Boehringer Ingelheim, Pfizer, Bristol Myers Squibb, and Abbott, outside of the submitted work. NP reports speaker honoraria from Vifor; consulting fees from Daiichi Sankyo; and travel funding from Bristol Myers Squibb and Pfizer, outside of the submitted work. GS reports travel support from Bayer, outside of the submitted work. SW reports personal fees from Amgen and Bayer, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Trial data can be made available on reasonable request to the corresponding author. Such requests must be accompanied by detailed study proposals, a description of study objectives, and a statistical analysis plan. Additional material might be requested during the assessments of the study eligibility for data sharing, which must be approved by the corresponding author (ie, sponsor-investigator of the trial), the trial steering committee, and the principal investigators of each centre. Each request will be checked for compatibility with regulatory (ethics committee) requirements as well as compatibility with patient informed consent.

Acknowledgments

We gratefully acknowledge the work of the data safety monitoring board and the clinical event adjudicators. This trial was funded by Swiss National Science Foundation (grant 140340), Swiss Heart Foundation, Stroke Funds Basel, University Hospital Basel, University of Basel, and Academic Society Basel.

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