# Aspirin vs anticoagulation in carotid artery dissection

## A study of 298 patients

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## ABSTRACT

**Background:** No randomized study has yet compared efficacy and safety of aspirin and anticoagulants in patients with spontaneous dissection of the cervical carotid artery (sICAD).

**Methods:** Prospectively collected data from 298 consecutive patients with sICAD (56% men; mean age 46 ± 10 years) treated with anticoagulants alone (n = 202) or aspirin alone (n = 96) were retrospectively analyzed. Admission diagnosis was ischemic stroke in 165, TIA in 37, retinal ischemia in 8, and local symptoms and signs (headache, neck pain, Horner syndrome, cranial nerve palsy) in 80 patients, while 8 patients were asymptomatic. Clinical follow-up was obtained after 3 months by neurologic examination (97% of patients) or structured telephone interview. Outcome measures were 1) new cerebral ischemic events, defined as ischemic stroke, TIA, or retinal ischemia, 2) symptomatic intracranial hemorrhage, and 3) major extracranial bleeding.

**Results:** During follow-up, ischemic events were rare (ischemic stroke, 0.3%; TIA, 3.4%; retinal ischemia, 1%); their frequency did not significantly differ between patients treated with anticoagulants (5.9%) and those treated with aspirin (2.1%). The same was true for hemorrhagic adverse events (anticoagulants, 2%; aspirin, 1%). New ischemic events were significantly more frequent in patients with ischemic events at onset (6.2%) than in patients with local symptoms or asymptomatic patients (1.1%).

**Conclusions:** Within the limitations of a nonrandomized study, our data suggest that frequency of new cerebral and retinal ischemic events in patients with spontaneous dissection of the cervical carotid artery is low and probably independent of the type of antithrombotic treatment (aspirin or anticoagulants). ***Neurology*® 2009;72:1810–1815**

## GLOSSARY

**CI** = confidence interval; **DSA** = digital subtraction angiography; **ICH** = intracranial hemorrhage; **IST** = International Stroke Trial; **MCA** = middle cerebral artery; **MRA** = magnetic resonance angiography; **NIHSS** = National Institutes of Health Stroke Scale; **OR** = odds ratio; **PSV** = peak systolic velocity; **RI** = resistance index; **sICAD** = spontaneous dissection of the cervical carotid artery; **sVAD** = spontaneous vertebral artery dissection.

Approximately 2.5% of ischemic strokes are caused by spontaneous extracranial internal carotid artery dissection (sICAD); this proportion is considerably higher in stroke patients under the age of 50.[1,2] The antithrombotic treatment of choice in patients with sICAD remains unclear, as this issue has not yet been examined in a controlled randomized trial. Thus, treatment decisions in patients with acute sICAD are currently empirical.

We undertook this study to evaluate the incidence and predictors of ischemic events and adverse events of antithrombotic therapy in patients with first sICAD treated with aspirin alone or anticoagulants alone for at least 3 months after the initial diagnosis.

**METHODS** Prospectively collected data of consecutive patients with sICAD treated from December 1987 to November 2005 in the Neurological Departments of the University Hospitals of Bern and Zürich, Switzerland, were retrospectively analyzed. The

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**Table 1** Baseline characteristics in patients with spontaneous dissection of the cervical carotid artery treated with anticoagulants alone or aspirin alone

| | Anticoagulants | Aspirin | *p* |
|---|---|---|---|
| No. | 202 | 96 | |
| Age, y, mean ± SD | 46 ± 10 | 46 ± 11 | 0.9* |
| Sex (men/women) | 115/87 | 53/43 | 0.8† |
| Arterial hypertension | 56 (27.7) | 25 (26) | 0.8† |
| Diabetes mellitus | 2 (1) | 0 (0) | 0.3‡ |
| Hypercholesterolemia | 61 (30.2) | 34 (35.4) | 0.4† |
| Smoking current | 53 (26.2) | 37 (38.5) | 0.03† |
| Smoking former | 14 (6.9) | 9 (9.4) | 0.4† |
| Smoking (current/former) | 67 (33.2) | 46 (47.9) | 0.01† |
| Coronary artery disease | 1 (0.5) | 1 (1) | 0.6‡ |
| Peripheral artery disease | 1 (0.5) | 0 (0) | 0.5‡ |
| Diagnostic modality | | | |
| Cervical MRI | 155 (77) | 78 (81) | |
| DSA | 21 (10) | 8 (9) | 0.7† |
| Cervical MRI and DSA | 26 (13) | 10 (10) | |
| Ischemic stroke | 118 (58.4) | 47 (49) | 0.1† |
| Transient ischemic attack | 25 (12.4) | 12 (12.5) | 1.0† |
| Amaurosis fugax | 7 (3.5) | 1 (1) | 0.2† |
| Local symptoms and signs | 45 (22.3) | 35 (36.5) | 0.01† |
| Asymptomatic | 7 (3.5) | 1 (1) | 0.2‡ |
| IV thrombolysis | 2 (1) | 10 (10.4) | 0.5‡ |

Values are n (%) unless noted otherwise.
*Mann-Whitney *U*-test.
†$\chi^2$ test.
‡Fisher exact test.
DSA = digital subtraction angiography.

protocol of this study was approved by the Ethical Committees of both universities.

**Baseline investigations.** All patients underwent an assessment of vascular risk factors, physical and neurologic examinations, quantification of the neurologic deficit with the National Institutes of Health Stroke Scale (NIHSS) score, routine blood tests, 12-lead electrocardiography, and ultrasound studies of the cerebral arteries. NIHSS score was assessed retrospectively, using hospital records, in patients recruited before 1989 (n = 12). Neuroradiologic examinations comprised MRI of the neck with or without three-dimensional time of flight magnetic resonance angiography (MRA), intra-arterial digital subtraction angiography (DSA), or both. Additionally, cranial CT, MRI, or both were performed in patients presenting with ischemic stroke or TIA.

**Diagnosis of sICAD.** Diagnosis of sICAD was based on the detection of mural hematoma in the cervical ICA on fat-suppressed MRI sequences, on characteristic MRA or DSA findings (flame-shaped occlusion, string sign, segmental stenosis beginning distal to the carotid bulb or aneurysm of the cervical carotid artery), or both.[3] In patients with occlusion of the cervical ICA on angiography, diagnosis of sICAD was confirmed by MRI detection of a mural hematoma; details of diagnostic workup in the two treatment groups are provided in table 1.

Only patients with spontaneous carotid dissection were enrolled in this study. Carotid dissection was classified as spontaneous when occurring spontaneously or secondary to a precipitating event such as coughing, abrupt head movement, or a minor neck or head trauma.[4]

**Inclusion and exclusion criteria.** Patients were included in the present study if they had had their first sICAD and were treated either with aspirin alone or anticoagulants alone. Patients initially treated with aspirin and subsequently anticoagulants were not further evaluated. This was also the case in patients who had their ICAD while on aspirin and were thereafter treated with oral anticoagulants. The same was true for patients who did not receive any antithrombotic treatment. Patients with ischemic stroke, TIA, or retinal ischemia (amaurosis fugax or retinal infarction) were only evaluated if antithrombotic treatment was initiated within 24 hours of symptom onset. The sole exception was for patients who underwent IV thrombolysis, in whom treatment was initiated 24 hours after completion of thrombolytic treatment.

Recurrent sICADs in patients already enrolled in this study (defined as reported previously[3]) were not evaluated. The same was true for patients who underwent surgical treatment (n = 6), endovascular treatment (n = 10), or both (n = 1) during the study period.

**Vascular risk factors.** The following vascular risk factors were assessed: current cigarette smoking; former cigarette smoking, defined as abstention from cigarette smoking that started more than 5 years ago[5]; arterial hypertension; diabetes mellitus; hypercholesterolemia; and history of coronary and peripheral artery disease.

**Ultrasound studies.** Hemodynamic status (no stenosis, stenosis ≤50%, stenosis 51–80%, stenosis >80%, and occlusion) of the cervical ICA was assessed as reported previously.[6] Stenoses of the cervical ICA were quantified as follows[3,6]: a ≤50% stenosis was diagnosed when intrastenotic peak systolic velocity (PSV) was 91–120 cm/s in women and 81–120 cm/s in men, and the PSV quotient intrastenotic ICA/contralateral cervical ICA >1.12. A >50% stenosis was diagnosed when intrastenotic PSV was >120 cm/s and the PSV quotient intrastenotic ICA/CCA on the side of ICAD (ipsilateral) >1.5. Intrastenotic velocities are frequently decreased in sICAD causing high-grade stenosis.[7] Therefore, to avoid falsely negative findings, >80% stenoses were only diagnosed using prestenotic and poststenotic hemodynamic criteria, whereby at least two of the following had to be present: 1) the ratio of the resistance index (RI; PSV − peak end diastolic velocity/PSV) ipsilateral CCA/RI contralateral CCA >0.15; 2) reversed flow in the ipsilateral ophthalmic artery; 3) crossflow through the anterior communicating artery.

**Antithrombotic treatment.** The type of antithrombotic treatment was chosen by the treating neurologist in all cases. No selection criteria toward aspirin or anticoagulants were applied. Before the publication of the results of the International Stroke Trial (IST) in 1997,[8] most patients with sICAD were treated with anticoagulants. Following the publication of the IST results, many attending neurologists started treating patients with acute ischemic stroke caused by sICAD with aspirin. Oral anticoagulation was always initiated while the patient was receiving IV heparin (target thrombin time I >200, thrombin time II 10–20 seconds). IV heparin was discontinued after INR was found to be within therapeutic range on two subsequent days. Before the publication of the IST results, the aspirin dose used ranged between 100 and 300 mg/day. After the publication of

IST, both departments started using 300 mg/day for the first 2 weeks after sICAD diagnosis and 100 mg thereafter.

**Follow-up/outcome measures.** Patients were instructed to report to the Neurological Clinic on an emergency basis if they experienced any symptoms suggestive of a recurrent cerebral or retinal ischemia or any new local symptoms. Clinical follow-up was obtained after 3 months by neurologic examination (n = 274; 97%) or a structured telephone interview (n = 8; 3%), which was performed by a neurologist.

Outcome measures were 1) new cerebral or retinal ischemic events, defined as ischemic stroke, TIA, transient monocular blindness, or retinal infarction; 2) symptomatic intracranial hemorrhage (ICH), defined as neurologic deterioration ≥4 points on the NIHSS and evidence of appropriately located intracranial hemorrhage on CCT, MRI, or both; and 3) major extracranial bleeding, defined as clinically overt bleeding resulting in a drop in the hemoglobin level of at least 2 g/dL or necessitating transfusion of two or more units of red cells.

**Statistical analysis.** Normally distributed data were expressed as mean ± SD and compared using unpaired *t* test; non-normally distributed data were expressed as median (95% confidence interval [CI]) and compared using Mann-Whitney *U*-test. Distribution of frequencies was examined using $\chi^2$ or Fisher exact test as appropriate.

Influence of antithrombotic treatment (aspirin or anticoagulants) on the incidence of recurrent cerebral ischemic events, treatment complications, or both was assessed using univariate analysis. It was technically not possible to test for an interaction between antithrombotic treatment and symptomatic status (ischemic stroke, TIA, and retinal ischemia vs only local symptoms and signs and asymptomatic) in a multiple regression model, because the number of events was too low. Therefore, we performed multiple logistic regression analysis using antithrombotic treatment and symptomatic status as variables and subsequently compared the odds ratios (OR) to those acquired by univariate analysis. Significance was declared at $p < 0.05$.

**RESULTS** A total of 355 patients were diagnosed with sICAD during the study surveillance period. Seventeen patients were excluded because of surgical treatment (carotid endarterectomy, n = 4; extra-intracranial bypass surgery, n = 2), endovascular treatment (intra-arterial thrombolysis, n = 4; carotid stenting followed by intra-arterial thrombolysis, n = 4; occlusion of aneurysm by coiling, n = 1; middle cerebral artery [MCA] stenting, n = 1), or both (extra-intracranial bypass surgery followed by balloon occlusion of the internal carotid artery, n = 1). Thirty-two patients were excluded because of medical treatment decisions (aspirin followed by warfarin, n = 30; no antithrombotic treatment, n = 2). Change of antithrombotic drug was initiated by the general practitioner or neurologist responsible for outpatient treatment and was not the result of treatment complications or recurrent ischemic events in any patient. No recurrent ischemic events occurred in these 30 patients during the 3-month follow-up period. Eight patients (age 49 ± 7 years, admission NIHSS score 22 ± 9) died of malignant MCA infarction within the first 7 days after symptom onset, leaving 298 patients for further evaluation. These were 168 (56%) men and 130 women, aged 46 ± 10 years. Of these, 202 (68%) were treated with heparin and warfarin alone and 96 (32%) with aspirin alone. A bilateral sICAD was diagnosed in 17 (6%; contralateral sICAD was asymptomatic in all cases) and additional unilateral spontaneous vertebral artery dissection (sVAD) in 18 (6%) patients. Admission diagnosis was ischemic stroke in 165 (55%), TIA in 37 (12%), and retinal ischemia in 8 (3%) patients. Only local symptoms and signs located on the side of the symptomatic sICAD, such as head or neck pain, pulsatile tinnitus, Horner syndrome, or cranial nerve palsy, were diagnosed in 80 (27%) patients, while remaining 8 (3%) patients had an asymptomatic sICAD accompanying a symptomatic sVAD.

Demographic data and vascular risk factors were not significantly different in the 210 (70%) patients presenting with cerebral ischemic symptoms (ischemic stroke, TIA, retinal ischemia) compared to the 88 (30%) patients in whom sICAD caused either merely local symptoms or was asymptomatic. Still, significant differences in the degree of carotid stenosis were observed between the two groups (table 2). Furthermore, antithrombotic treatment was different, as a significantly higher proportion of patients with sICAD causing local or no symptoms was treated with anticoagulants. Only smoking was significantly different in the vascular risk profiles between the two treatment groups (baseline characteristics listed in table 1).

During the 3-month follow-up period, one patient had an ischemic stroke (0.3%), 10 (3.4%) a TIA, and 3 (1%) a retinal ischemia (amaurosis fugax in all cases). The ischemic stroke occurred in a patient with left sICAD initially symptomatic with a TIA (global aphasia and right hemiparesis) on the third day of treatment with IV heparin. Clinical symptoms comprised global aphasia and right hemiplegia (NIHSS score 15). Four TIAs occurred in patients treated with IV heparin, 3, 4, 13, and 16 days after onset of initial symptoms (thrombin time II was within target range in two patients and too low in the remaining two patients) and four in patients treated with warfarin 20, 25, 36, and 47 days after onset of initial symptoms. Two TIAs occurred in patients treated with aspirin 9 and 89 days after onset of initial symptoms. Finally, three patients had an amaurosis fugax while treated with IV heparin (n = 1; 2 days after onset of initial symptoms) or with warfarin (n = 2; 13 and 53 days after onset of initial symptoms). All cerebral ischemic events occurred in the territory supplied by the dissected internal carotid artery.

**Table 2** Baseline characteristics in patients with spontaneous dissection of the cervical carotid artery presenting with and without ischemic symptoms of the brain or retina

| | Cerebral or retinal ischemic symptoms | | |
|---|---|---|---|
| | Present | Absent | p |
| No. | 210 | 88 | |
| Age, y, mean ± SD | 46 ± 10 | 47 ± 10 | 0.3* |
| Sex (men/women) | 114/96 | 54/34 | 0.3† |
| Arterial hypertension | 59 (28.1) | 22 (25) | 0.6† |
| Diabetes mellitus | 2 (1) | 0 (0) | 0.4‡ |
| Hypercholesterolemia | 73 (34.8) | 22 (25) | 0.1† |
| Smoking current | 66 (31.4) | 24 (27.3) | 0.5† |
| Smoking former | 20 (9.5) | 3 (3.4) | 0.07† |
| Smoking (current/former) | 86 (41) | 27 (30.7) | 0.1† |
| Coronary artery disease | 1 (0.5) | 1 (1.1) | 0.5‡ |
| Peripheral artery disease | 1 (0.5) | 0 (0) | 0.5‡ |
| Dissected cervical carotid artery | | | |
| No stenosis | 15 (7.1) | 27 (30.7) | |
| Stenosis ≤50% | 6 (2.9) | 12 (13.6) | <0.00001† |
| Stenosis >50–80% | 9 (4.3) | 12 (13.6) | |
| Stenosis >80% and occlusion | 180 (85.7) | 37 (42) | |
| Median baseline NIH Stroke Scale score (95% confidence interval) | 11 (10-12) | 0 | |
| Anticoagulants | 150 (71.4) | 52 (59.1) | |
| Aspirin | 60 (28.6) | 36 (40.9) | 0.04† |
| IV thrombolysis | 12 (5.7) | — | |

Values are n (%) unless noted otherwise.
*Mann-Whitney *U*-test.
†$\chi^2$ test.
‡Fisher exact test.

**Table 3** New ischemic events and adverse events of antithrombotic therapy in patients with spontaneous dissection of the cervical carotid artery treated with anticoagulants alone or aspirin alone

| | Anticoagulants | Aspirin | p* |
|---|---|---|---|
| No. | 202 | 96 | |
| New ischemic events | 12 (5.9) | 2 (2.1) | 0.1 |
| Ischemic stroke | 1 (0.3) | 0 (0) | 0.5 |
| Transient ischemic attack | 8 (4) | 2 (2.1) | 0.4 |
| Retinal ischemia | 3 (1.5) | 0 (0) | 0.2 |
| Total adverse events† | 4 (2) | 1 (1) | 0.4 |
| Symptomatic ICH | 2 (1) | 0 (0) | 0.3 |
| Major extracranial bleeding | 2 (1) | 1 (1) | 1 |
| Total events | 16 (7.9) | 3 (3.1) | 0.1 |

Values are n (%).
*Fisher exact test.
†For definitions of adverse events, see text.
ICH = intracranial hemorrhage.

Frequency of recurrent ischemic events was 5.9% in patients treated with anticoagulants and 2.1% in patients treated with aspirin ($p = 0.1$, Fisher exact test; OR 3.0 [0.7–13.5], $p = 0.2$). Frequency of recurrent ischemic events was higher in patients presenting with cerebral ischemic symptoms (13/210; 6.2%) compared to patients with only local symptoms or asymptomatic patients (1/88; 1.1%); this difference narrowly missed significance ($p = 0.06$, Fisher Exact test; OR 5.7 [0.7–44.6], $p = 0.1$). In a multiple logistic regression including main effects of treatment and symptomatic status, the OR for the treatment effect was estimated as 2.6 (0.6–12.1) ($p = 0.2$) and the OR for symptomatic status as 5.2 (0.7–40.9) ($p = 0.1$).

A symptomatic ICH occurred in two patients treated with anticoagulants and in none of the patients treated with aspirin: one patient developed generalized epileptic seizures 17 days after initial symptom onset; CCT scan revealed an ICH in the infarcted area. A second patient with left sICAD and ischemic stroke in the territory of the left middle cerebral artery (initial NIHSS score 15) developed a moderate contralateral hemiparesis (NIHSS score 20) 11 days after onset of initial symptoms; CCT revealed a right frontal hemorrhage. Two patients had an extracranial hemorrhage while being treated with IV heparin (hemorrhage in rectus abdominis with Hb drop from 10.2 to 7.4 mg/L in the first patient and traumatic hemorrhage in right thigh and lower leg after sport injury with Hb drop from 12.8 to 10.7 mg/L in the second patient), while one patient treated with aspirin had recurrent nosebleeds with Hb drop from 13.1 to 11 mg/L. None of these patients required a blood transfusion. Frequency of recurrent cerebral ischemic and treatment adverse events is displayed in table 3.

**DISCUSSION** The first interesting finding of the present study was the low overall frequency of new ischemic events in patients with sICAD, irrespective of antithrombotic medication; only one patient (0.3%) had an ischemic stroke, while the combined frequency of TIA and transient retinal ischemia was merely 4.4%. All recurrent ischemic events occurred in the territory of the dissected carotid artery. Nearly identical findings concerning the prevalence of ischemic stroke were reported in a study examining a historical cohort of 432 patients with cervical artery dissection (0.3% per year; 0.2% within the first 3 months after diagnosis).[9] The same study, however, reported a 0.6% per year overall prevalence of TIA; only one TIA occurred within the first 3 months after diagnosis. This observation could be due to the fact that retrospective assessment of hospital charts and telephone interviews were used to obtain

follow-up data. It is thus possible that some TIAs were not registered.

We observed a markedly lower frequency of new ischemic events in patients with ICAD presenting merely with local symptoms or in asymptomatic patients, treated with antithrombotics for primary stroke prevention, as compared to patients with ICAD presenting with ischemic symptoms. This finding suggests that the natural course of ICAD in patients without cerebral or retinal ischemic symptoms at presentation is benign, thus highlighting the importance of separating these two groups of patients with sICAD in future studies. Significant differences in the degree of carotid stenosis between the two groups constitute the most probable explanation for this observation, although an influence of the more frequent use of oral anticoagulants in patients presenting only with local symptoms or in asymptomatic patients cannot be excluded.

No controlled randomized trial has yet compared the efficacy or safety of aspirin and anticoagulation in patients with sICAD. Two recent meta-analyses found no significant difference between the two treatments.[10,11] Our results are in accordance with these reports; frequency of recurrent ischemic events and of treatment adverse events did not significantly differ between patients treated with aspirin and those treated with anticoagulants. Oral anticoagulation is more expensive than aspirin, more cumbersome for the patients, limits the patient's lifestyle, requires a higher degree of compliance, and is dependent on frequent laboratory tests that themselves carry the risk of misinterpretations that in particular circumstances might increase the risk of secondary ischemia due to overdosing of heparin and increase in the wall hematoma.[12] Thus, treatment of patients with sICAD with oral anticoagulants would only be justified in the presence of significant differences in efficacy, which were not observed in the present study. We must note, however, that this study was not powered to detect differences between the two treatment groups, as the frequency of recurrent cerebral ischemic events was low. A prospective, randomized trial would be necessary to resolve this issue. Based on our results, 440 patients with sICAD should be enrolled in each treatment group to detect a significant difference in the rate of recurrent cerebral ischemic events at the 5% level with a power of 80%. While such study would be of great interest, it would also be particularly challenging, considering the fact that the annual incidence of sICAD ranges from 1.7 to 3.0 per 100,000 inhabitants.[13-15] Considering the fact that only one patient had an ischemic stroke during the follow-up period and none died, it becomes obvious that a much higher number of patients would be needed if the study endpoints were death or dependency; a recent review estimated this count as 2,800.[16]

The present study has some obvious limitations. First, treatment allocation was not randomized and evaluation of recurrent ischemic events not blinded. Furthermore, warfarin was the drug of choice up to 1997, with aspirin being predominantly prescribed in the last 8 years of the study. While this reduces the scientific validity of our results, it must be pointed out that the two groups of patients were similar in their clinical characteristics and treatment decisions based on the discretion of the attending neurologist, without any formal rules for patients' allocation. Second, both primary (ICAD causing no cerebral ischemia) as well as secondary (ICAD causing ischemia) stroke prevention were investigated. However, separate analysis of the two patient subgroups also failed to demonstrate significant differences between the treatment groups. Third, the number of patients evaluated in this study was relatively small. It must be noted, however, that we included all patients diagnosed with sICAD in two university hospitals with a catchment area of approximately 2 million people over 18 years. Fourth, allocation to treatment changed over time, with patients recruited in the early years of the study mostly being treated with warfarin and recently recruited patients predominantly being treated with aspirin. Fifth, we can provide no data on potential neurologic deterioration within the initial 24 hours after symptom onset and thus cannot exclude that one of the two treatments would have been more efficient during this time period. Finally, due to the long duration of patient recruitment, different examination techniques were used for diagnosing sICAD; this fact constitutes a further, albeit inevitable, methodologic drawback of our study.

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