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Stroke 2007;38:2605-2611; originally published online Jul 26, 2007;

DOI: 10.1161/STROKEAHA.107.489666

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214
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ISSN: 1524-4628

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Antiplatelets Versus Anticoagulation in Cervical Artery Dissection

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Background and Purpose—The widespread preference of anticoagulants over antiplatelets in patients with cervical artery dissection (CAD) is empirical rather than evidence-based.

Summary of Review—This article summarizes pathophysiological considerations, clinical experiences, and the findings of a systematic metaanalysis about antithrombotic agents in CAD patients. As a result, there are several putative arguments in favor as well as against immediate anticoagulation in CAD patients.

Conclusions—A randomized controlled trial comparing antiplatelets with anticoagulation is needed and ethically justified. However, attributable to the large sample size which is required to gather meaningful results, such a trial represents a huge venture. This comprehensive overview may be helpful for the design and the promotion of such a trial. In addition, it could be used to encourage both participation of centers and randomization of CAD patients. Alternatively, antithrombotic treatment decisions can be customized based on clinical and paraclinical characteristics of individual CAD patients. Stroke severity with National Institutes of Health Stroke Scale score ≥ 15 , accompanying intracranial dissection, local compression syndromes without ischemic events, or concomitant diseases with increased bleeding risk are features in which antiplatelets seem preferable. In turn, in CAD patients with (pseudo)occlusion of the dissected artery, high intensity transient signals in transcranial ultrasound studies despite (dual) antiplatelets, multiple ischemic events in the same circulation, or with free-floating thrombus immediate anticoagulation is favored. (*Stroke*. 2007;38:2605-2611.)

Key Words: anticoagulation ■ antiplatelets ■ antithrombotic treatment ■ cervical artery ■ dissection ■ stroke

In younger stroke patients, cervical artery dissection (CAD) is considered among the most important stroke etiologies.^{1,2} A recent population-based study observed an average annual incidence rate of 2.6 (95% CI, 1.86 to 3.33) per 100 000 inhabitants.³ Extracranial internal carotid artery dissection (eICAD) can be expected in about 1.7 to 3.0/100 000 per year.³⁻⁵ For extracranial vertebral artery dissection (eVAD), the average annual incidence was reported to be 0.97 (95% CI, 0.52 to 1.4) per 100 000, indicating that eICAD can be expected twice as often as eVAD.³ However, according to the observations of the Canadian Stroke Consortium, eVAD was even more common than eICAD.⁶

The recurrence rate of stroke in CAD is $< 1\%$ per year,^{3,7-10} except for familial cases. It is still debated whether in CAD patients anticoagulation or antiplatelet agents are superior, balancing risk and benefits of either approach.¹¹⁻¹³ Anticoagulation is widely advocated.¹⁴⁻¹⁶ However, evidence from randomized trials on the efficacy of this therapy is missing.¹⁷⁻¹⁹

Nevertheless, physicians still have to decide whether individual CAD patients should receive immediate anticoagulation or antiplatelet agents in order to prevent (recurrent) stroke. Facing this dilemma, we render a comprehensive overview about pathophysiological observations and clinical experiences with both treatment options including

Received March 29, 2007; accepted April 17, 2007.

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Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.107.489666

a systematic metaanalysis of the existing clinical data on antithrombotic therapy in eICAD. Eventually, a synopsis summarizes features in favor versus against early anticoagulation in CAD.

Pathophysiological Arguments in Favor of Anticoagulation in Extracranial CAD

Extracranial CAD occurs when blood penetrates through a subintimal tear into the arterial wall leading to intramural hematoma. Blood accumulation can occur subadventitially, which may result in local compression syndromes or in subarachnoid hemorrhage, the latter being more frequent in intracranial than in extracranial dissections. Alternatively, mural hematoma can result in arterial narrowing causing stenosis or vessel occlusion that may lead to cerebral ischemia. Stroke in CAD is a consequence either of embolism originating from the injured intima or of hemodynamic compromise.

Several arguments support an embolic mechanism, such as the observation of microemboli, the occurrence of distal branch occlusions, and the infarct lesion pattern on brain scans. Indeed, transcranial doppler monitoring studies revealed microembolic signals downstream of the dissected arteries. In eICAD, high intensity transient signals (HITS) suggesting embolism were detected in the middle cerebral artery.^{20–24} Similarly, in eVAD, HITS were shown in the posterior cerebral artery.²⁰ The frequency of HITS in CAD patients is reported within the range of 25% to 60%.^{20–24} However, sample sizes of 6 to 28 patients limit the significance of these numbers.

Conventional angiography studies in eICAD patients visualized occlusions of branches of the anterior or middle cerebral arteries in several patients.^{25–27} The frequency of this angiographic finding has been reported within a range of 14% (5/36),²⁵ 16% (3/19),²⁶ and even 50% (4/8).²⁷

Analyses of the infarct lesion pattern on CT or T2-weighted MRI in eICAD stroke patients revealed that the vast majority had cortical, large subcortical or mixed cortical-subcortical lesions. Only 3% to 16% had borderzone lesions according to most studies.^{28–31} Similar findings were reported in a mixed population of eICAD and eVAD.³² Only 1 group reported contrary results with nearly 50% borderzone infarcts.³³ More recently, diffusion-weighted MRI, revealed that 10 of 14 (71%) eICAD patients had multiple diffusion-weighted MRI lesions.³⁴ These findings suggest that in most patients, artery-to-artery embolism rather than hemodynamic compromise is the main underlying mechanism in stroke attributable to eICAD.

In analogy to cardioembolic stroke (eg, atrial fibrillation), where anticoagulation is superior to antiplatelets (eg, aspirin) in secondary stroke prevention,³⁵ these observations would favor anticoagulation in stroke prevention of CAD. However, the assignability to CAD patients is questionable. Conclusions by analogy from atherosclerotic carotid artery disease are limited because of the younger age and the different pathomechanism in CAD patients.

Little is known about the significance of the degree of stenosis in eICAD (or eVAD) and the risk of thromboembolism. High-grade stenoses and occlusion attributable to eI-

CAD seem more likely to cause ischemic events, whereas eICAD without lumen narrowing seems to lead to more local symptoms.³⁶ In addition, pilot data suggest different diffusion-weighted MRI lesion patterns in eICAD patients with occluded ICA compared with those with stenotic ICA.³⁷ These observations support the idea that the degree of hemodynamic compromise is associated with the extent of the thromboembolic risk in CAD.

Another, at least theoretical, argument in favor of anticoagulation is the risk of clot formation in cases of arterial occlusion attributable to CAD. Cases with free-floating thrombi in dissected internal carotid arteries have indeed been reported.^{38,39} In addition, most occluded arteries recanalize over time, 30% within 8 days, 60% to 80% within 3 months.^{40,41} During the recanalization process, clots may be mobilized and transported downstream, where they can cause blockage of intracranial arteries prompting embolic infarctions.⁴²

Furthermore, in a rat model of transient focal cerebral ischemia, steady plasma concentrations of unfractionated heparin reduced infarct volume and prevented inflammatory damage.⁴³ Thus, immediate IV heparin may be neuroprotective.⁴³ However, it remains to be shown that such beneficial effects are translatable to human stroke and especially to stroke attributable to CAD.

Pathophysiological Arguments Against Anticoagulation in Extracranial CAD

CAD is characterized by intramural accumulation of blood. At least theoretically, anticoagulation may lead to enlargement of the mural bleed because both heparin and warfarin inhibit coagulation. In case of anticoagulation-mediated perpetuation or recurrence of intramural bleeding, increase of the outer vessel diameter may cause local compression symptoms, such as painful Horner syndrome or cranial nerve palsies. More important, hemodynamic worsening can occur, which implies the risk of low-flow infarcts. Recent reports clarified that such a complication is not a mere theoretical concern.^{44–46} Dreier et al reported on delayed occlusion of the internal carotid artery during heparin therapy in 5 of 20 patients with eICAD.⁴⁴ The activated partial thromboplastin time ratio was significantly higher in patients with delayed ICA occlusion (2.6 ± 0.4) versus those without (2.0 ± 0.5).⁴⁴ Thus, the likelihood for delayed ICA occlusion seems to increase with higher degrees of anticoagulation. Delayed ICA occlusion was also observed in a lightweight CAD patient during unplanned overanticoagulation.⁴⁵ Although the direct evidence of an extended mural hematoma was lacking in both publications, it was speculated that (relative) overshooting anticoagulation may have caused mural rebleeding, which caused ongoing lumen narrowing leading to complete ICA occlusion. Whether the relationship between anticoagulation and delayed carotid occlusion is causal rather than coincidental requires further studies. Furthermore, it remains to be determined how often delayed occlusion may occur with antiplatelets.

Interestingly, delayed loss of arterial patency during IV heparin was not associated with clinical worsening in most of these patients.^{44,45} However, one of these patients developed

a watershed infarct.⁴⁴ He was the only one without sufficient collateralization at the circle of Willis, suggesting a hemodynamic stroke mechanism.

In addition, a recent metaanalysis showed that for acute stroke patients in general, immediate anticoagulation had neither short- nor long-term benefit.⁴⁷ Furthermore, in acute cardioembolic stroke initial anticoagulation was associated with a 2.89 (95% CI, 1.19 to 7.01) increase in symptomatic intracranial bleedings compared with aspirin or placebo according to an updated metaanalysis.⁴⁸ Based on the results of the Warfarin versus Aspirin in Secondary Stroke Prevention (WARSS) study, anticoagulation does not seem more effective than antiplatelets to prevent further ischemic events after stroke of arterial origin.⁴⁹ Likewise, the Joint Stroke Guideline Development Committee of the American Academy of Neurology and the American Stroke Association recommended not to use early anticoagulation in acute ischemic stroke irrespective of the underlying etiology ("IV, unfractionated heparin or high-dose low molecular heparin/heparinoids are not recommended for any specific subgroup of patients with acute ischemic stroke that is based on any presumed stroke mechanism . . . because data are insufficient").⁵⁰

In CAD patients with severe strokes, immediate anticoagulation may be potentially hazardous. This theoretical concern is based on findings of an increased rate of symptomatic hemorrhagic transformation in severe strokes in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) trial.⁵¹ Applying general American Stroke Association (ASA) guidelines for anticoagulation,⁵² immediate anticoagulation in CAD stroke patients with National Institutes of Health Stroke Scale score of 15 or more cannot be recommended.

Clinical Experiences With Antiplatelets and Anticoagulation in CAD

Observational Data About Intracranial Hemorrhage in CAD

CAD commonly results in ischemic stroke, transient ischemic attacks or local compression symptoms. However, it can also cause subarachnoid hemorrhage,⁶ though this is more frequent in intracranial dissections. Among the 116 CAD patients reported by the Canadian stroke consortium, 4 (3%) patients had subarachnoid hemorrhages⁶ with a trend toward eVAD predominance over eICAD. Likewise, there are single case reports about eVAD presenting with subarachnoid hemorrhage.^{53,54} However, this feature is unusual and should prompt the search for an accompanying intracranial dissection. The latter leads to subarachnoid hemorrhage in 20% of patients.³²

The aforementioned observations of subarachnoid hemorrhage in CAD patients urge toward CT- or MR-imaging of the brain before any antithrombotic treatment, most notably before anticoagulation. Furthermore, intracranial extension of CAD seems a feature arguing against anticoagulation.¹¹

In eICAD, the risk of intracranial hemorrhages as a treatment complication seems to be low with either antithrombotic agent. In a systematic metaanalysis across case series, 2 of 414 (0.5%) patients on anticoagulation and none

of 157 patients with antiplatelets had intracranial hemorrhages.¹⁹ However, nonrandomized studies are known to be highly susceptible to bias, and outcome events may be underrepresented.⁵⁵ Taking into account that even thrombolysis has been used in eICAD patients without bleeding complications,⁵⁶ the absolute risk of symptomatic hemorrhage attributable to anticoagulation in CAD is not expected to be high. As a limitation, this assumption is based on uncontrolled data.

Observational Data About (Recurrent) Cerebral Ischemia in CAD

Some patients with stroke attributable to CAD report preceding warning symptoms mostly within a week before the index stroke.^{57–59} This observation implies that there might be a chance to prevent stroke in such patients. However, this optimistic view is clouded by the fact that in half of these patients the interval between inaugural symptoms and stroke is only in the magnitude of minutes to hours.⁵⁸

CAD patients who present with stroke have HITS more often than CAD patients with pure nonischemic signs and symptoms.²¹ In addition, most CAD patients with recurrent ischemia have HITS (ie, 6/7,²³ and 3/3,²⁰ respectively). These observations may indicate that CAD patients with HITS have an increased stroke risk attributable to assumed embolism and require stronger antithrombotic therapy. However, HITS occur also despite antithrombotic therapy.^{20,24} Furthermore, no association was recorded between the presence or number of HITS and the type of antithrombotic treatment (ie, anticoagulants or antiplatelets).²⁴ Among a population of 20 CAD patients, all 5 HITS-positive ones had some form of antithrombotic therapy during transcranial doppler monitoring. This was heparin in 3, aspirin in 1, and aspirin plus heparin in another patient, respectively.²⁰

In HITS originating from atherosclerotic carotid artery stenoses, cessation of HITS was associated with antiplatelets rather than with anticoagulants.⁶⁰ The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial data showed that the combined antiplatelet therapy with aspirin plus clopidogrel⁶¹ reduced HITS in carotid stenosis of atherosclerotic origin. Whether this can be translated for CAD patients is unclear. Interestingly, in a single case observation of a CAD patient, HITS associated with recurrent ischemic events persisted despite dual antiplatelet therapy combined with IV heparin. After the addition of IV dextran 40, HITS were no longer detectable. After dextran was stopped, symptoms recurred. HITS were re-detected and again disappeared with IV dextran.⁶² Thus, though the presence of HITS seems to identify a subgroup of patients with particular high risk of (recurrent) cerebral ischemia, the best preventive means remains to be determined.

Stroke occurrence or recurrence has been reported in eICAD patients treated with antiplatelets,^{15,59} as well as in those with sufficient anticoagulation,^{40,63–65} indicating that the avoidance of first or recurrent stroke even with anticoagulation is not granted. The studies summarized in a systematic review published in 2003¹⁹ showed no evidence that antiplatelets are less effective than anticoagulants in preventing stroke in eICAD patients. However, solely in 5 studies, strokes under antithrombotic therapy were reported with

details on the applied therapy. Whereas in 1 study stroke occurred in 6 of 8 patients with antiplatelets, other studies did not report similar observations but reported stroke under anticoagulation in 3% to 16% of their patients. Three of 91 patients (3.3%) with “no antithrombotic therapy” had a first or recurrent stroke. Although this percentage is higher than for patients treated with antiplatelets (1.8%) or anticoagulants (1.8%), it does not necessarily reflect the assumed benefits of antithrombotic treatment. The differences may as well reflect a bias, such as that “no antithrombotic treatment” could have been primarily applied to patients considered to have a poor prognosis.

Among the 105 treated CAD patients of the Canadian Stroke Consortium, the annual recurrence rate for stroke, transient ischemic attacks, or death as combined end point was higher in the aspirin group (12.4%) compared with the anticoagulated group (8.3%).⁶ However, in a Mexican series of 130 CAD patients, 14% of the anticoagulated eICAD patients versus 7% of the aspirin-treated eICAD patients had a recurrent stroke.⁵⁹ In another recent case series of >100 CAD patients, stroke during follow-up was recorded in neither treatment group. However, recurrent transient ischemic attacks occurred in only 1 of 113 CAD patients with anticoagulation, compared with 6 of 9 patients with antiplatelets. In turn, 1 anticoagulated patient experienced symptomatic intracerebral hemorrhage, whereas none of the patients with antiplatelets did so.⁵⁸ These findings illustrate the need to balance risk and benefits of either agent in a comprehensive way. Even in the absence of randomized controlled trials, a systematic metaanalysis of the available data can provide clinically useful information about the effects in CAD patients treated either with anticoagulants or with antiplatelets.

Systematic Metaanalysis About Antithrombotic Drugs for eICAD

The systematic metaanalysis aimed, firstly, to determine whether antithrombotic drugs (antiplatelet drugs, anticoagulation) are effective and safe in eICAD patients, and, secondly, which is the better treatment.¹⁹ In the absence of controlled trials, a systematic review was done by comprehensive analyses of nonrandomized studies with ≥ 4 patients which reported on outcomes with stratification to antiplatelets versus anticoagulants (ie, full dose IV or SC fractionated or unfractionated heparin or oral coumarin). Primary outcomes were “dead from all causes” and “dead or disabled” at the end of the follow-up period. Secondary outcomes include stroke occurrence or recurrence, any stroke during reported follow-up, extracranial hemorrhage, and intracranial hemorrhage.

No reliable comparisons of antiplatelets or anticoagulants with control (ie, “no antithrombotic treatment”) were available. For comparative analyses of both agents, 26 studies including 327 patients (who either received antiplatelets or anticoagulants) were eligible.^{15,25,40,63–85}

Two of 109 patients (1.8%) treated with antiplatelets and 4 of 218 (1.8%) treated with anticoagulants were reported dead, respectively. The weighted estimates across studies show that the likelihood of death does not differ between both treatment groups as indicated by a Peto odds ratio of 1.59 (95% CI, 0.22 to 11.59).

The analysis of the outcome “dead or disabled” was based on 20 studies.^{25,63–65,68–79,81,82,84,85} Fourteen of 59 patients (23.7%) treated with antiplatelets were dead or disabled, compared with 17 of 119 (14.3%) patients treated with anticoagulants. These discrepant frequencies, which are based on accumulated events irrespectively of the studies they were derived from, seem to indicate a trend in favor of anticoagulants. However, the weighted estimate across all studies reveals that such an impression was misleading. The Peto odds ratio of 1.94 with a wide 95% CI of 0.76 to 4.91 clarifies that there is no significant difference in the odds of being “dead or disabled” among both treatments groups. Further details including the findings on secondary outcomes can be found in the Cochrane Review.¹⁹

Randomized Controlled Trial

Summarizing the aforementioned pathophysiological considerations, the observational data, and the results of the systematic metaanalysis, a large randomized controlled trial (RCT) comparing anticoagulants and antiplatelets is desirable and ethically justified. Its protocol should include a stringent definition of dissection, a standardized diagnostic protocol, strictly random allocation to different types of antithrombotic treatment, as well as accurate unbiased assessment of outcome. The trial designer should consider that both treatment groups are balanced in clinical symptoms (ie, stroke versus transient ischemic attacks versus pure local compression symptoms), stroke severity, in the degree of vessel patency,³⁶ and in the rate of thrombolized patients, as to date there are no data to support denial of thrombolysis in CAD-patients.⁵⁶ In addition, the ratio of eICAD to VAD within both treatment groups should be the same, as both may differ in the frequencies of recurrences⁸⁶ or bleeding risks.⁶ Treatment onset should be as early as possible because recurrent ischemic events seem to be most frequent within the first days to weeks.⁸⁶ On the basis of the presented data we estimate a sample size of at least 1400 patients in each treatment arm in order to detect a 5% difference in the proportion of patients dead or disabled from 20% to 15% (a 25% relative odds reduction).¹⁹ Such an RCT is likely to face difficulties in obtaining funding, recruiting centers and patients, as shown in the Rapid Anticoagulation Prevents Ischemic Damage (RAPID) study. This multinational, academic trial compared aspirin versus IV heparin in acute nonlacunar stroke (<12 hours) irrespectively of the etiology. It had to be stopped because just 67 patients were randomized in 30 months.⁸⁷ Nevertheless, in CAD a large RCT is important and could solve the decades-long debate whether to use immediate anticoagulation. Indeed, a UK-based feasibility study is about to start.⁸⁸ If possible, randomization of CAD patients in such an RCT is encouraged. In case RCTs in CAD may prove to be not feasible, participation in multicenter registries⁸⁹ makes sense. In such registries systematically ascertained data can be collected including comprehensive information about outcome stratified to the applied antithrombotic agent. Comparative analyses of these data may serve as means to approximate best medical treatment in CAD. Furthermore, such data can be included in future updates of the systematic metaanalysis.

Clinical and Paraclinical Features as Putative Arguments Against or in Favor of Immediate Anticoagulation in Individual CAD Patients at the Time of Diagnosis

Against Immediate Anticoagulation	Comment/References
Severe strokes, ie, NIHSS score ≥ 15	In analogy to findings of increased rate of symptomatic hemorrhagic transformation in severe strokes in TOAST. ⁵¹ Applying general ASA guidelines for anticoagulation. ⁵²
No brain imaging available	CAD can present with bleedings. ^{53,54} Applying general ASA guidelines for anticoagulation. ⁵²
Accompanying intracranial dissection	Bleeding risk seems \uparrow in intracranial dissection, ³² eg, vertebral artery dissection.
Local compression syndromes without stroke/TIA	Subadventitial dissection may have less risk for ischemic events. ³⁶
Concomitant diseases with increased bleeding risk (extra/intracranial)	Translating atrial fibrillation studies to CAD. ⁹⁰
Insufficient intracranial collaterals	Delayed ICA occlusion under heparin. ^{45,46} Watershed infarct in a patient without collaterals. ⁴⁴ However, low intracranial flow may favor anticoagulants to prevent intracranial thrombus formation.
In Favor of Immediate Anticoagulation	Comment/References
HITS despite (dual) antiplatelets	HITS more frequent in patients with recurrent ischemia. ^{20,23} Few studies. HITS surrogate marker of "microclots"?
Occlusion/ pseudo-occlusion	Embolization may occur during recanalization. ⁴²
Multiple TIAs/strokes affecting multiple regions (same circulation)	Clinical course may suggest repetitive emboli
Free-floating thrombus	Rare finding ^{38,39}

In the absence of evidence-based treatment guidelines, this synopsis is based on pathophysiological considerations, observations and conclusions by analogy and reflects the view of the authors. Neither clinical/paraclinical features nor the comments/references claim to be exhaustive.

TIA indicates transient ischemic attack; ASA, American Stroke Association; NIHSS, National Institutes of Health Stroke Scale.

Conclusion

This overview about pathophysiology, clinical observations, and the systematic metaanalysis provide several putative arguments in favor as well as against immediate anticoagulation in CAD patients. Thus, a randomized controlled trial comparing antiplatelets with anticoagulation is needed and ethically justified. However, because of the large sample size which is required to gather meaningful results, such a trial is a huge venture. Therefore, until evidence-based data are available, the Table may be clinically useful for individual treatment allocations as it summarizes putative arguments in favor versus against immediate anticoagulation of CAD.

Disclosures

None.

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