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Review Article

Review of Toward Individual Treatment in Cervical Artery Dissection: Subgroup Analysis of the TREAT-CAD Randomized Trial

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Abstract

Cervical artery dissection (CeAD) is a leading cause of ischemic stroke in young adults, with a mean age of approximately 45 years. In hospital-based cohorts, nearly two-thirds of patients with CeAD present with cerebral ischemia, most commonly ischemic stroke or transient ischemic attack. Despite its relative rarity in the overall stroke population, CeAD therefore carries a substantial individual and societal burden.

Keywords: Cervical artery dissection, Cerebral ischemia, Intravenous thrombolysis, Anticoagulation

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Why Cervical Artery Dissection Still Matters

Cervical Artery Dissection (CeAD) is a leading cause of ischemic stroke in young adults, with a mean age of approximately 45 years [1,2]. In hospital-based cohorts, nearly two-thirds of patients with CeAD present with cerebral ischemia, most commonly ischemic stroke or transient ischemic attack [3,4]. Despite its relative rarity in the overall stroke population, CeAD therefore carries a substantial individual and societal burden [5,6].

Beyond the initial event, patients remain at risk for recurrent events [7,8]. In STOP-CAD, the largest observational study to date, subsequent ischemic stroke occurred in 4.4% of patients within six months.4 In the randomized-controlled TREAT-CAD trial, the combined endpoint of clinical or MR-imaging endpoints occurred in 19% (33/173) of patients in the per-protocol population.9 Most notable, all subsequent ischemic strokes occurred between day 1 and day 7, indicating that the stroke risk is particularly high in the first days after diagnosis [9,10]. Highlighting the importance of very early and sufficient secondary prevention in patients with CeAD.

Secondary prevention in CeAD relies on antithrombotic therapy, either antiplatelet agents or anticoagulation. Persistent uncertainty regarding the optimal regimen prompted two randomized trials-CADISS11 and TREAT-CAD9-which compared antiplatelet therapy with vitamin K antagonist-based anticoagulation and found no clear superiority of either approach [9,11]. These results were confirmed by a study-level meta-analysis [12].

Consequently, current clinical guidelines continue to recommend both regimens, antiplatelet and anticoagulation therapy, as viable options for stroke prevention in CeAD. However, the guidelines still do not provide clear recommendations on when to prefer one treatment over the other, despite the remarkable variability in patient presentation and individual risk profiles [13-15].

Rationale for subgroup analyses in CeAD

CeAD is a heterogeneous disease with variability in clinical presentation and risk of subsequent ischemia. Observational studies consistently show that baseline characteristics such as cerebral ischemia at presentation, occlusion of the dissected artery and early CeAD recurrence increase stroke risk [16]. However, whether the effect of antithrombotic therapy differs across such patient profiles cannot be reliably addressed in non-randomized settings due to confounding by indication.

To explore whether specific patient characteristics modify treatment effects, we performed prespecified and exploratory subgroup analyses using patient-level data from the randomized TREAT-CAD trial. The overarching goal was to identify patient profiles that might inform more individualized antithrombotic strategies in CeAD.

Introduction

TREAT-CAD was a multicenter, randomized, open-label, noninferiority trial with blinded endpoint adjudication. Adults with symptomatic carotid or vertebral artery dissection confirmed by MRI were randomized within 14 days of symptom onset to receive either aspirin (300 mg daily) or anticoagulation with vitamin K antagonists for 90 days, with recommended heparin bridging until a target INR of 2-3 was achieved.

The primary endpoint was a composite of clinical outcomes (ischemic stroke, major extracranial or intracranial hemorrhage, or death at 90 ± 30 days) and imaging outcomes (new ischemic or hemorrhagic brain lesions on MRI at 14 ± 10 days) [17]. In the per-protocol population (n=173), the primary endpoint occurred in 23.1% of patients treated with aspirin and in 14.6% treated with anticoagulation. Aspirin did not meet the prespecified criterion for noninferiority, nor did anticoagulation reach superiority.

Methods

Subgroup analyses were performed in the per-protocol population to ensure inclusion of patients with centrally verified CeAD who received the allocated treatment. Based on prior literature, patients were stratified according to the following predefined dichotomous baseline characteristics.

- Presenting with cerebral ischemia-either clinical ischemic events (including transient ischemic attacks, amaurosis fugax, retinal infarction, and ischemic stroke), MRI lesions, or both-versus presenting with local symptoms only.
- Occlusion of the dissected artery at baseline defined as
- Flow or
- No-flow in contrast-enhanced MR angiography sequences, in line with prior research (no/yes).
- Early versus delayed treatment start (divided by the median of the study population at 6 days)
- Acute recanalization therapy (i.e., intravenous thrombolysis and/or endovascular therapy (no/yes); intracranial extension of the dissected artery (no/yes) [18,19].
- Intracranial extension of the dissected artery (no/yes) [20,21].
- Site of dissection defined as internal carotid artery dissection versus vertebral artery dissection.
- Single versus multivessel dissection [22].
- Younger versus older age (divided by the median of the study population at 47 years) [23].
- Male versus female sex [24].

Exploratory post hoc logistic regression models were used to assess treatment effects within each subgroup, with the composite primary endpoint serving as the outcome. Results are presented as odds ratios (ORs) with 95% confidence intervals. Given the exploratory nature of the analyses, no adjustment for multiple testing was applied.

Because nearly all outcome events (i.e., 32/33) occurred in patients presenting with cerebral ischemia, subgroup analyses were repeated in this higher-risk population.

Results

Outcome events were significantly more frequent in patients with arterial occlusion (16/55, 29% compared to no occlusion 16/117, 14%; p=0.03), those presenting with cerebral ischemia (32/118, 28% compared to those with local symptoms only 1/55, 2%; =<0.001), and those who underwent acute recanalization therapy (11/23, 48% compared to those without 22/150, 15%; p=<0.001). No differences were observed for early versus delayed treatment initiation or intracranial extension of the dissection, sex, or the dichotomized age [25].

A differential treatment effect was observed for arterial occlusion only. Among patients without occlusion, anticoagulation was associated with lower odds of clinical or MRI outcomes compared with aspirin (OR 0.28, 95% CI 0.07-0.86). No such effect was observed in patients with occlusion [25].

Among the patients presenting with cerebral ischemia, anticoagulation was associated with lower odds of outcome events in those without occlusion, those treated early, and those without intracranial extension. Across all other subgroups, no clear treatment effect modification was detected.

Clinical implications and future directions

These findings support the hypothesis that CeAD comprises distinct risk phenotypes that may benefit from different antithrombotic strategies. Patients presenting with isolated local symptoms appear to be at very low risk for recurrent ischemia. In contrast, patients with cerebral ischemia represent a higher-risk group in whom treatment effects may differ.

Although exploratory, our results suggest that anticoagulation may be preferable in selected patients with CeAD-particularly those presenting with cerebral ischemia but without arterial occlusion or intracranial extension. Confirmation in adequately powered randomized trials is essential and should target those high-risk patients for subsequent ischemic events.

- Restricting inclusion to patients presenting with cerebral ischemia.
- Randomizing patients in the hyperacute phase.
- Stratifying randomization by validated risk profiles (especially occlusion of the dissected artery).

Take-to-work message

In CeAD patients presenting without signs of cerebral ischemic the risk of subsequent stroke is most likely low, indicating that aspirin treatment may be sufficient. In turn, in CeAD patients presenting with cerebral ischemia, anticoagulation might be preferable to aspirin, possibly in particular within selected clinical subgroups (e.g., absence of an intracranial extension of the dissection). These findings are hypothesis-generating and require validation, but they support a shift away from a uniform treatment approach toward more individualized antithrombotic decision-making.

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