Commentary on the Cervical Artery Dissection in Stroke Study Trial

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The incidence of cervical artery dissection (CeAD) in the general population is as low as 2.6 to 3.0 per 100,000 inhabitants per year and accounts for only a small proportion of all ischemic stroke, but it is a major cause of stroke among young and middle-aged adults. Cervicocerebral dissection was the second common cause (15%) preceded by cardioembolism (20%) in 1008 Finnish patients with ischemic stroke aged 15 to 49 years.

The current guidelines recommend antithrombotic treatment at the acute phase of CeAD, especially in patients presenting with ischemic stroke or transient ischemic attack. However, the optimal strategy for prevention of stroke in patients with acute CeAD is controversial, and there is a lively debate around choice of antithrombotic drugs (anticoagulation versus antiplatelet therapy), duration of antithrombotic treatment, and indications for endovascular and surgical treatments.

The recent Cervical Artery Dissection in Stroke Study (CADISS) trial published in the Lancet Neurology aimed to address one of these questions, namely, which antithrombotic therapy, out of anticoagulation or antiplatelet agents, should be preferred at the acute phase of CeAD. Many practitioners routinely treat CeAD patients with anticoagulants, and some guidelines are supporting this practice, mainly based on the empirical argument that the mechanism of ischemic stroke in CeAD is thromboembolic in the vast majority of cases (an assumption derived from the neuroimaging distribution of ischemic lesions).

**Summary of the CADISS Trial Results**

The CADISS trial was planned as a phase 2 feasibility trial. Patients with CeAD (extracranial carotid or vertebral artery dissection) with onset of symptom within the past 7 days and imaging evidence of definite or probable dissection were included. The sample size required for this feasibility phase was estimated at 250 based on the rates of recurrence reported in observational studies (details on the underlying assumptions, eg, on the rate of ischemic events and difference in treatment effect, are not presented). The authors preplanned that, based on the data obtained from the feasibility phase, a decision would be made about whether to perform a definitive phase 3 trial.

After analysis of the feasibility trial results, the authors decided not to pursue with a phase 3 trial. Indeed, the results of the phase 2 trial suggest that, using the end point of stroke, death, or major bleeding, a sample size of 10,000 participants would be required (representing several years of recruitment by hundreds of stroke centers). CADISS investigators reported no difference in efficacy of antiplatelet and anticoagulant drugs at preventing stroke and death in this feasibility phase, and importantly, they found that stroke occurrence was rare in both groups, much rarer than they expected. Indeed, 3 of 126 (2%) patients under antiplatelet agents versus 1 of 124 (1%) patients under anticoagulants sustained a recurrent stroke within 3 months (odds ratio, 0.33 [95% confidence interval, 0.01–4.23]; P=0.63). There were no deaths, but 1 major bleed occurred in the anticoagulation group (subarachnoid hemorrhage).

**Had CADISS Investigators Overestimated the Risk of Recurrent Stroke in the Study Population?**

The original sample size estimation of the definite phase 3 trial by the CADISS investigators was based on a Cochrane systematic review in 2003, which included 327 patients from 26 small observational studies and showed no statistically significant difference between the 2 treatments. At least 1400 patients in each treatment arm were assumed to be needed. Of note, in a later Cochrane systematic review in 2010 (posterior to the CADISS protocol design), comprising 1262 patients from 36 observational studies, rates of recurrent stroke were lower (1.9% with anticoagulation and 2.0% with antiplatelet therapy). In that review, at least 8000 patients (4000 in each arm) were estimated to be required for detecting a 1% difference, if it exists, in the recurrence rate. In line with these findings, the reported rates of recurrent stroke were low (ranging from 0.3% to 2.9% for a 3- to 12-month period), in the 3 largest published cohorts, with ≤982 patients. Contrasting these findings, a recent comparatively smaller cohort of 250 patients with acute ischemic stroke or transient ischemic attack from...
the German stroke study collaboration (ie, hospitalized in expert stroke units) reported a higher cumulative risk of subsequent stroke of 10.7% at 1 year. Differences in type and timing of presenting symptoms and in recruitment modalities (eg, whether through tertiary center) may explain, at least partly, inconsistencies among studies. A much higher stroke risk during follow-up has been observed in patients with ischemic symptoms at admission than those with local symptoms only as confirmed in the CADISS trial. The latter included mostly CeAD patients with stroke or transient ischemic attack (n=224), as well as CeAD patients with local symptoms only (n=26), and 19 study subjects had already experienced recurrence before recruitment.

Overall, publications posterior to the CADISS trial design suggest that CADISS investigators had overestimated the stroke recurrence rate in CeAD patients.

Of note, mean time between symptom onset and randomization was 3.4 days in the anticoagulation arm and 3.9 days in the antiplatelet therapy arm in the CADISS trial. Restricting enrollment to patients presenting with ischemic symptoms, with earlier recruitment and randomization, may have led to different results. The success of the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) trial, with mean time from onset to randomization of 13 hours, is an example highlighting the importance of early recruitment for a stroke prevention study. Moreover, the CADISS trial itself showed that all recurrent ischemic events occurred early after the dissection, within the first 10 days after randomization. However, reducing time from symptom onset to confirmation of CeAD diagnosis remains a challenge in some centers.

Was It Appropriate to Use the Information From the Phase 2 Feasibility CADISS Trial to Estimate the Sample Size of a Future Phase 3 Trial?

The main objective of this phase 2 feasibility CADISS trial was to enable accurate estimation of the stroke recurrence rate and thereby to calculate a sample size for a definitive phase 3 trial. In many cases, pilot studies are conducted to generate data for sample size calculations. This seems especially reasonable in situations where there are no data from previous studies. For CeAD, data from multiple observational studies comparing the outcome of patients taking anticoagulants versus antiplatelet therapy are available, but these have biases inherent to the observational, retrospective design. Of note, caution is warranted when using pilot studies to estimate treatment effects, as such estimates may be unrealistic/biased because of the limited sample size.

Was the Aim of the CADISS Trial to Examine the Effectiveness or Efficacy of the Treatment?

By definition, an efficacy trial tests whether the treatment effect is true in an ideal setting and the effectiveness trial tests whether the treatment is working in a broader real-world setting. The major question of the effectiveness trial is whether the true treatment effect can be generalizable. Therefore, many important components of the effectiveness trial are pragmatic and the treatment effect is assumed to be true and unquestionable even in a narrower sense.

Many aspects of the CADISS trial were in accordance with the definition of an effectiveness trial. The choice of antiplatelet drugs was at the discretion of the local physicians (dual antiplatelet therapy was prescribed in 44% of patients), and the quality of anticoagulation in the anticoagulation arm (targeting an international normalized ratio between 2 and 3) was not reported unlike in other anticoagulation trials. Moreover, diagnosis of dissection was made by the local investigators without standardized predefined diagnostic criteria but followed by a central review of imaging after inclusion in the trial. The latter failed to confirm CeAD diagnosis in 20% of patients. Although the authors rightly comment that this reflects the high diagnostic error rate for CeAD in routine clinical practice and although per-protocol analyses yielded similar results, this may have contributed to dilute a potential treatment effect with other pragmatic aspects of the CADISS trial.

What We Learned From CADISS: Considerations for Future Trials

Overall, this first randomized trial comparing antiplatelet agents to anticoagulants at the acute phase of CeAD, despite the aforementioned limitations related to the design as a pragmatic feasibility trial, has the important merit of highlighting 2 main difficulties inherent to clinical trials on this condition: (1) the low rate of ischemic events under any antithrombotic treatment in a prospective randomized setting; and (2) the persistent high rate of diagnostic inaccuracies despite well-validated and published diagnostic criteria. Whether future efforts to perform randomized trials comparing antithrombotic strategies at the acute phase of CeAD are warranted remains an open question. Effect size estimates derived from the CADISS trial and from the largest recent observational cohort studies are discouraging. Power might be somewhat improved by selecting patients at the highest risk of recurrent events, for example, patients who already sustained an ischemic event, by reducing the interval between symptom onset and randomization and by conducting central verification of diagnostic criteria at inclusion, with more homogeneous antiplatelet protocols and strict monitoring of anticoagulation levels. However, numbers required for a phase 3 trial would likely still be extremely large. Further information may be obtained from the ongoing Biomarkers and Antithrombotic Treatment in Cervical Artery Dissection (TREAT-CAD) trial, run in Switzerland, that incorporates in the outcome the presence of novel silent cerebrovascular lesions (ischemia on diffusion-weighted imaging, microbleeds or macrobleeds on T2* imaging) on follow-up magnetic resonance imaging, in addition to recurrent clinical stroke (clinicaltrials.gov: NCT02046460). This may increase the number of events, but the clinical significance of these silent lesions will be a point of discussion. Meanwhile, the debate on which antithrombotic treatment to preferentially prescribe for acute CeAD patients remains open.

As emphasized by others, antiplatelet treatment is less costly, more convenient, and seemed safer in the CADISS trial although the difference was not significant and, as acknowledged by the authors, the trial was not designed and powered

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to demonstrate superiority of anticoagulants over antiplatelets. A good news for CeAD patients is that, in line with the largest published observational studies, available randomized data (although not definitive) show a low rate of recurrent ischemic events within 3 months of CeAD onset, under any antithrombotic treatment.

Disclosures
None.

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