Thrombolitics, Anticoagulants, and Antiplatelet Agents

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More than 250 articles regarding thrombolytic therapy in acute ischemic stroke were published in the first 10 months of 2005 (Source PubMed). In this section we will focus on some reports that directly affect and improve the treatment of stroke patients, that led to further phase III trials, or that represent a great disappointment after several years of investigation.

Thrombolitics

The key publication on thrombolytic therapy in acute ischemic stroke using recombinant tissue plasminogen activator was published almost 10 years ago, which led to the approval of this drug in many countries. Since then, considerable knowledge has been gained about the risks and benefits of thrombolytic therapy. However, 1 major concern is still the limited time window of 3 hours. Many studies have been conducted to extend this time window without increasing the risk for the patients. In addition, more pathophysiologically oriented imaging techniques, such as diffusion- and perfusion-weighted imaging, seemed to be able to detect tissue at risk for further infarction. In January 2005, the results of the Desmoteplase In Acute Ischemic Stroke trial (DIAS) were published. DIAS was a dose-finding, phase II, randomized trial designed to evaluate the safety and efficacy of intravenous desmoteplase, a highly fibrin-specific thrombolytic agent, administered within 3 to 9 hours of ischemic stroke onset in patients with perfusion/diffusion mismatch on MRI. It was the first randomized, double-blind, placebo-controlled thrombolysis trial using MRI-based criteria for patient selection and also as an end point. The efficacy end points were rate of reperfusion on MRI after 4 to 8 hours and clinical outcome as assessed by National Institutes of Health Stroke Scale Score (NIHSSS; ≤8-point improvement or scoring of 0 or 1), modified Rankin scale (0 to 2), and Barthel Index (75 to 100) at 90 days. Safety end points were rate of symptomatic intracranial hemorrhage (sICH) and mortality. Altogether 107 patients were included. The trial was halted after the first 47 patients treated with a fixed dose not adjusted for body weight because of an excessive rate of sICH in the verum group (26.7%) and redesigned as a dose escalation trial with body weight adjustment (62.5, 90, or 125 μg/kg bw). Thereafter, only 1 of 45 patients suffered from sICH (2.2%). Reperfusion rates of up to 71.4% were observed in patients who received desmoteplase (125 μg/kg) compared with 19.2% in patients given placebo (P=0.0012). Favorable 90-day clinical outcome was found in 22.2% of placebo-treated patients and between 13.3% (62.5 μg/kg; P=0.757) and 60.0% (125 μg/kg; P=0.009) of desmoteplase-treated patients. Interestingly, early reperfusion correlated favorably with clinical outcome (P=0.0028): outcome was favorable in 52.5% of patients experiencing reperfusion versus 24.6% of patients without reperfusion. As a consequence of these promising results, a phase III trial was initiated in the summer of 2005.

As an alternative strategy for opening intracranial vessels, several mechanical devices are under investigation. Data from a prospective, nonrandomized, multicenter trial investigating an embolectomy device (Merci Retriever) used within 8 hours after stroke onset symptoms in 151 patients ineligible for intravenous tissue plasminogen activator were recently published. Recanalization was achieved in 48% (68/141) of patients in whom the device could be deployed. Clinically significant procedural complications developed in 10 of 141 (7.1%) patients. sICH was observed in 11 of 141 (7.8%) patients, and a good neurological outcome (modified Rankin score of 2 or less) was observed more frequently at 90 days in patients in whom recanalization was successful than in patients in whom it was not (46% versus 10%; P<0.0001). Meanwhile, the US Food and Drug Administration has approved the use of the Merci Retriever for acute embolic stroke, and a number of other similar strategies are presently under various stages of investigation.

Anticoagulants

In February 2005 further results of the efficacy of the oral thrombin inhibitor Ximelagatran in prevention of stroke in patients with nonvalvular atrial fibrillation (AF) were published. The phase III trials of Ximelagatran in AF, SPORTIF III and V, found that a fixed oral dose of Ximelagatran (36 mg twice daily) was comparable to dose-adjusted warfarin (international normalized ratio 2.0 to 3.0) in preventing stroke and systemic thromboembolic complications among high-risk patients with AF. Results from the population of >7000 patients in SPORTIF III and V demonstrate noninferiority of Ximelagatran compared with warfarin. Indeed, data from SPORTIF III show an absolute reduction of 1.6% per year in stroke and systemic embolic events with Ximelagatran as compared with 2.3% per year with warfarin (P=0.10). SPORTIF V further supports noninferiority between the 2 agents with an absolute risk reduction of 0.45%, which is well...
within the predefined noninferiority margin (95% CI, −0.13, 1.03; \( P=0.13 \)). Although event rates for major bleeding did not differ significantly between Ximelagatran and warfarin in either study, combined rates for major and minor bleeding were significantly lower with Ximelagatran. The overall net clinical benefit, taking into account effects on stroke or systemic embolic events, major bleeding, and death, was also greater with Ximelagatran than with warfarin in both studies. Elevated serum transaminase enzymes were observed in \( \approx 6\% \) of patients given Ximelagatran in these trials. This, together with an increased rate of coronary artery disease, were the main reasons why the FDA denied approval of Ximelagatran in this indication.\(^5\)

Since the International Stroke Trial (IST), heparin has been used increasingly less often in acute stroke patients because of an unbalanced risk to benefit ratio.\(^6\) Recently, a very promising article was published on the use of unfractionated heparin in acute stroke patients.\(^7\) Some 418 selected patients were randomly treated within 3 hours after stroke onset with intravenous heparin sodium (aPTT ratio 2.0 to 2.5) or saline for 5 days. Safety end points were death, sICH, and major extracranial bleedings by 90 days of stroke; the efficacy end point was a modified Rankin score 0 to 2 at 90 days. In the heparin group the rate of sICH was significantly increased (6.2% versus 1.4%; \( P=0.008 \)). Despite this increased bleeding risk, a significantly higher proportion of self-independent patients with at 90 days was found among the heparin-treated patients (38.9% versus 28.6%; \( P=0.025 \)). This positive effect is of particular interest because the mean NIHSSS at randomization was 17 in both treatment groups. In the light of these results, we may have to reconsider our therapeutic strategies for patients in whom thrombolytic therapy is contraindicated within a 3-hour time window.

**Antiplatelet Agents**

**Another Funeral of a Good Friend?**

Over the last 5 years, the GpIIb/IIIa-antagonist Abciximab was evaluated for treating patients with acute ischemic stroke. A dose-escalation study had determined that a regimen of Abciximab administered as a 0.25 mg/kg intravenous bolus followed by a 12-hour infusion at 0.125 \( \mu \)g/kg per minute (maximum 10 \( \mu \)g/min) could be given safely.\(^3\) In April 2005 the results of the Phase II AbESTT study were published.\(^9\) The primary safety outcome parameter of this randomized, double-blind, placebo-controlled trial with 400 patients treated within 6 hours after onset of ischemic stroke was the rate of sICH. This occurred in 7 of 195 (3.6%) patients treated with Abciximab and 2 of 199 (1%) patients given placebo (odds ratio 3.7; 95% CI, 0.7 to 25.9; \( P=0.09 \)). In the phase II trial treatment with Abciximab showed a nonsignificant shift in favorable outcomes as measured by modified Rankin scale scores at 3 months (odds ratio 1.20; 95% CI, 0.84 to 1.70; \( P=0.33 \)). Reanalysis of the data showed some significant results, particularly for the patients treated within the first 5 hours after symptom onset, eg, modified Rankin scale 0 to 1 was found in 53.9% of the Abciximab and 34.6% of the placebo patients (\( P=0.013 \)).

As a conclusion, a larger phase III trial (AbESTT-II) was initiated, aiming to randomize 1800 patients. Of them 1200 subjects were meant to be randomized as the primary population within 4.5 hours after stroke onset and a second group of 600 later than 4.5 hours or 2.5 hours after awakening with stroke symptoms.

In May 2005, the inclusion of patients awakening with stroke symptoms was stopped because of an increased risk of intracranial hemorrhage in that population. At that time, the independent Safety and Efficacy Monitoring Committee (SEMC) recommended continuing enrollment. Unfortunately, however, beginning in October 2005, trial sponsors announced that enrollment in the AbESTT-II study had been temporarily suspended, and on October 28, 2005, enrollment into AbESTT-II was terminated definitely as per an SEMC recommendation. After reviewing these recommendations, the principal investigators, the AbESTT-II Executive Committee, and the sponsors unanimously agreed with the SEMC and stopped the trial.\(^10\) At this timepoint 808 patients had been enrolled into Abestt-II. The exact reasons for the SEMC decision have not been published yet. However, it can be anticipated that Abciximab will no longer play a prominent role in acute stroke treatment. The consequences for other trials using Abciximab (eg, ROSIE\(^1\)) cannot be anticipated at this time.

**References**


**Key Words:** antihypertensive agents • anticoagulants • thrombolytic therapy
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*Stroke*. 2006;37:312-313; originally published online January 12, 2006; doi: 10.1161/01.STR.0000200560.01068.65
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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