Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised controlled trial

Sanne M Zinkstok, Yvo B Roos, on behalf of the ARTIS investigators

Summary

Background Thrombolysis with intravenous alteplase is the only approved treatment for acute ischaemic stroke. After alteplase-induced recanalisation, reocclusion occurs in 14–34% of patients, probably because of platelet activation. Early administration of antiplatelet therapy after alteplase could reduce the risk of reocclusion and improve outcome. We compared the effects of early addition of intravenous aspirin to alteplase with standard alteplase without aspirin.

Methods In this multicentre, randomised, open-label trial with blind-endpoint assessment, patients with acute ischaemic stroke treated with alteplase were randomly assigned to 300 mg intravenous aspirin within 90 min after start of alteplase treatment or to no additional treatment. In both groups, oral antiplatelet therapy was started 24 h after alteplase treatment. The primary endpoint was favourable outcome, defined as a score of 0–2 on the modified Rankin scale at 3 months. This trial is registered with the Netherlands Trial Register (NTR822).

Findings Between July 29, 2008, and April 20, 2011, 642 patients (322 patients aspirin, 320 patients standard treatment) of the targeted 800 patients were enrolled. At that time, the trial was terminated prematurely because of an excess of symptomatic intracranial haemorrhage (SICH) and no evidence of benefit in the aspirin group. At 3 months, 174 (54·0%) patients in the aspirin group versus 183 (57·2%) patients in the standard treatment group had a favourable outcome (absolute difference –3·2%, 95% CI –10·8 to 4·2; crude relative risk 0·94, 0·82 to 1·09, p=0·42). Adjusted odds ratio was 0·91 (95% CI 0·66–1·26, p=0·58). SICH occurred more often in the aspirin group (14 [4·3%] patients) than in the standard treatment group (five [1·6%]; absolute difference 2·8%, 95% CI 0·2–5·4; p=0·04). SICH was more often the cause of poor outcome in the aspirin group compared with the standard treatment group (11 vs 1, p=0·006).

Interpretation Early administration of intravenous aspirin in patients with acute ischaemic stroke treated with alteplase does not improve outcome at 3 months and increases the risk of SICH. The results of this trial do not support a change of the current guidelines, which advise to start antiplatelet therapy 24 h after alteplase.

Funding The Dutch Heart Foundation.

Introduction Intravenous thrombolysis with alteplase (or recombinant tissue plasminogen activator) is the only approved treatment for acute ischaemic stroke. After thrombolysis, the overall recanalisation rate is 46%. Reocclusion after initial recanalisation occurs in 14–34% of patients and is associated with clinical deterioration and poor outcome. Reocclusion has been attributed to increased platelet aggregation caused by the local thrombus, endothelial injury, and probably the thrombolytic treatment itself. Start of antiplatelet therapy early after alteplase might reduce the risk of reocclusion and thereby improve functional outcome. Indeed, previous use of antiplatelet therapy has been associated with higher rates of early recanalisation after thrombolysis. In the National Institute of Neurological Disorders and Stroke trial, clinical deterioration associated with poor outcome was less common in patients with previous use of antiplatelet therapy. In patients with acute myocardial infarction, the combination of antiplatelet therapy and thrombolysis reduces mortality substantially compared with thrombolysis alone.

In the ARTIS (Antiplatelet therapy in combination with Rt-PA Thrombolysis in Ischemic Stroke) trial, we compared the effects of early addition of 300 mg intravenous aspirin to alteplase with standard alteplase without aspirin.

Methods Study design and patients ARTIS was a prospective, multicentre, randomised, open-label trial with blinded endpoint assessment (PROBE design). The rationale and the protocol of the study have been published. The Department of Neurology of the Academic Medical Center (University of Amsterdam, Amsterdam, Netherlands) designed and coordinated the trial. 37 centres across the Netherlands participated (three academic hospitals, 20 non-academic teaching hospitals, and 14 non-teaching hospitals (see end of paper for ARTIS investigators)). Only centres with an annual thrombolysis rate above 20 could participate.
Patients were eligible if they were 18 years of age or older and were treated with alteplase for acute ischaemic stroke. Patients who had used antiplatelet therapy in the past 5 days before the stroke were excluded. Other exclusion criteria were known thrombocytopenia at presentation or a thrombocyte count of 100×10⁹ per L or less, contraindications to aspirin, anticoagulant therapy in the past 5 days, and legal incompetence before stroke.

The study protocol was approved by the medical ethics committees of all participating centres. All patients or their legal representatives provided written informed consent. The study was undertaken according to Good Clinical Practice standards, and was independently monitored by the Clinical Research Unit of the Academic Medical Center, University of Amsterdam.

This trial is registered with the Netherlands Trial Register (NTR822).

Randomisation and masking
The randomisation procedure was web-based (TENALEA Clinical Trial Data Management System). Randomisation was stratified for age (≤60 years, >60 years), sex, time between symptoms and start of alteplase treatment (<2 h, 2–3 h, >3 h), and centre with permuted blocks within strata. Due to large imbalances in treatment allocation because of an unexpectedly high number of participating sites, centres were removed as a stratification factor after inclusion of 465 patients (218 in the aspirin group and 247 in the standard treatment group), and the randomisation method was changed into a (non-deterministic) minimisation method balancing on age, sex, and time between symptoms and start of alteplase treatment. Local investigators and patients were not masked, but the research nurses who did the follow-up interviews were masked to treatment allocation.

Procedures
Patients were assigned, in a 1:1 ratio, to 300 mg intravenous aspirin (lysine acetylsalicylate, Aspégic, Sanofi-Aventis, Netherlands) within 90 min after start of alteplase treatment or to standard treatment with alteplase alone. Intravenous instead of regular oral administration was chosen to prevent exclusion of patients with dysphagia and to guarantee faster uptake. Intravenous aspirin was supplied by local hospital pharmacies. In both treatment groups, alteplase 0·9 mg/kg was administered within 4·5 h after symptom onset and oral antiplatelet therapy was initiated 24 h after alteplase according to international guidelines. Demographic and clinical characteristics were recorded at the time of enrolment. Stroke severity was measured with the National Institutes of Health Stroke Scale (NIHSS, range 0–42; higher scores reflect more severe deficit) at baseline and at 7–10 days (or at discharge if earlier). For all patients, a cranial CT scan was done before the start of alteplase treatment. In case of neurological deterioration, defined as an increase of 4 points or more on the NIHSS, a follow-up cranial CT scan was required. Any other brain imaging or diagnostic testing was left to the discretion of the local investigator. Trained and masked research nurses assessed functional outcome at 3 months with a structured telephone interview. Outcome was expressed as a score on the modified Rankin scale (mRs, range 0–5; higher scores reflect more severe disability with death rated as a score of 6). Patients or their relatives or caregivers were asked for recollection of treatment allocation after completing the interview.

The primary endpoint was favourable outcome at 3 months, defined as being independent (mRs 0–2), in accordance with the Cochrane analysis of thrombolysis in stroke. Secondary endpoints were mortality at 3 months, ordinal mRs score, NIHSS score at 7–10 days, symptomatic intracranial haemorrhage (SICH), and severe systemic bleeding. Causes of poor outcome were recorded. SICH was defined as neurological deterioration of 4 points or more increase on the NIHSS in combination with intracranial haemorrhage on follow-up CT scan without other obvious causes for the deterioration. All locally reported SICHS were centrally reviewed by the outcome assessment committee who had access to medical discharge letters and cranial CT scans. Severe systemic bleeding was defined as life-threatening bleeding requiring immediate medical intervention. Causes of poor outcome were categorised as a) initial ischaemic stroke including progression of initial stroke, b) recurrent

![Figure 1: Study profile](https://www.thelancet.com/assets/vol380/pdfs/0020-8385/v380-0521-f11.png)
ischaemic stroke, c) intracranial haemorrhage, d) other cerebral pathology, e) systemic ischaemic disease including myocardial infarction, f) systemic haemorrhage, g) other systemic pathology, and h) pre-existing poor functional status. Causes of poor outcome were centrally adjudicated after termination of the trial by an outcome assessment committee consisting of two neurologists, of which one was masked. In case of discrepancy between their judgments, a third masked neurologist was consulted. In patients with severe (progressive) stroke without any recovery, the cause of poor outcome was judged to be the initial ischaemic stroke. Patients with an mRs score of 3 or more due to permanent disability at time of the initial ischaemic stroke. Patients with an mRs score of 2 or less before stroke were additionally screened for haemorrhagic complications at the coordinating centre. The DSMB could advise the steering committee to stop the trial in case of safety concerns without prespecified stopping boundaries.

Besides safety monitoring a planned interim analysis for efficacy was done after follow-up assessment of the first 400 patients. In the DSMB charter, a predefined stopping rule for futility was formalised with a p value of 0.001 for treatment effect in favour of the treatment group according to the Haybittle-Peto approach. After the interim analysis, the reporting of the SAEs to the DSMB was reduced to once a month.

Statistical analysis
A 10% absolute increase in favourable outcome was classed as clinically relevant. On the basis of results of a Cochrane analysis and unpublished results from our own institution, we assumed that 50% of patients would have a favourable outcome. 400 patients per group (total 800 patients) were needed to have an 80% power with a two-sided significance level of 0.05 to detect a 10% increase in favourable outcome. Analyses were done on the basis of the intention-to-treat principle. Baseline characteristics and outcome parameters were summarised with descriptive statistics. The main analysis consisted of a single comparison between the treatment groups of the primary outcome (dichotomised mRs). Effect size was expressed in difference between proportions and percentages, crude relative risk (RR), and crude odds ratio (OR) estimates with 95% CIs. We additionally adjusted the primary outcome for clinically relevant baseline imbalances and factors used as stratifying variables during randomisation.

Results
Between July 29, 2008, and April 20, 2011, 642 patients were included in the trial of whom 564 had reached 3 months follow-up (figure 1). At that time, inclusion was prematurely halted according to the recommendation of the DSMB because of a significant difference of reported SICHs between the groups, with more SICHs in the aspirin group (safety). To investigate the possible

<table>
<thead>
<tr>
<th>Centre type (number of patients)</th>
<th>Aspirin (n=322)</th>
<th>Standard treatment (n=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic hospital</td>
<td>60</td>
<td>64</td>
</tr>
<tr>
<td>Teaching hospital</td>
<td>177</td>
<td>180</td>
</tr>
<tr>
<td>Non-teaching hospital</td>
<td>85</td>
<td>76</td>
</tr>
</tbody>
</table>

Table 1: Demographic and baseline characteristics
implications of this increased SICH rate, the results on the primary endpoint were revealed to the DSMB. On the basis of primary endpoint results of 564 patients, the DSMB recommended to the steering committee to stop the trial because there was no prospect of benefit in the aspirin group (futility). The steering committee concluded that although no significant overall worse outcome occurred, continuation of the trial was highly unlikely to result in benefit for the patients and therefore adopted the DSMB advice. Patient enrolment was therefore stopped on May 20, 2011.

There were 34 (11%) protocol violations in the aspirin group with most (22 [65%]) caused by a delay of aspirin administration (median delay 17 min [IQR 6–42]). Age, sex, independence before stroke, stroke severity, and number of patients per centre type (academic, teaching hospital, and non-teaching hospital) were equally distributed between treatment groups (table 1). In the aspirin group, slightly more patients had hypertension, diabetes, or previous stroke compared with the standard treatment group. Aspirin was administered at an average of 67 min after start of alteplase treatment.

At 3 months, the primary outcome was not different between groups: 54·0% (174 patients) in the aspirin group compared with 57·2% (183 patients) in the standard treatment group had a favourable outcome (absolute difference –3·2%, 95% CI —10·8 to 4·5; RR 0·94, 0·82–1·09; OR 0·88, 0·64–1·22, p=0·42). After adjustment for hypertension, diabetes, previous stroke, and the stratifying variables (sex, age, onset to treatment time, and centre type), adjusted OR was 0·91 (0·66–1·26, p=0·58). In patients with mRs score ≤2 before stroke (602 patients), RR was 0·94 (0·82–1·07, p=0·35; adjusted OR 0·88, 0·63–1·22, p=0·44).

Mortality was 11·2% (36 patients) in the aspirin group compared with 9·7% (31) in the standard treatment group (p=0·34). Among the survivors (mRs 0–5), Mann Whitney U analysis showed no different mRs scores between groups (p=0·86, figure 2). Incorporating deaths as mRs score of 5 showed the same results (p=0·85). At 7–10 days after baseline, neurological deficit of patients was similar in both groups: median NIHSS score 2 (IQR 0–7) in the aspirin group and 3 (1–7) in the standard treatment group (p=0·11).

More SAEs were reported in the aspirin group than in the standard treatment group (table 2). In the per-protocol analysis, 290 patients in the aspirin group and 325 in the standard treatment group were included (figure 1).

In the aspirin group, more patients had SICH than in the standard treatment group (absolute difference 2·8%, 95% CI 0·2–5·4; RR 2·78, 1·01–7·63, p=0·04). Most cases of SICH in both groups occurred within 36 h (12 in the aspirin group vs four in the standard treatment group, p=0·07, per-protocol analysis p=0·04). None of the patients diagnosed with SICH by local investigators had their diagnosis changed after central review. Severe systemic bleeding occurred in one patient in the aspirin group and in two in the standard treatment group.

Initial stroke was the main cause of poor outcome in both treatment groups (table 3). SICH was more often the cause of poor outcome in the aspirin group compared with the standard treatment group (11 vs 1, p=0·006). Of the 14 patients with SICH in the aspirin group (table 2), SICH was the cause of poor outcome in 11 patients, initial stroke in two, and one patient had no poor outcome. Of the five patients with SICH in the standard treatment group (table 2), SICH was the cause of poor outcome in one patient. Two patients in the standard treatment group had a pre-existing poor functional status, one patient had a severe initial stroke, and one patient had a traumatic intracerebral haemorrhage.

After the outcome assessment interview, 482 (75%) patients and caregivers were asked to recall treatment allocation. 339 (70%) of patients did not remember the treatment or made a wrong allocation choice.
Our SICH definition is similar to the definition used in these trials. By contrast with the alteplase trials, which required follow-up imaging in each patient, our low-budget and pragmatically designed trial requested only follow-up CT in case of neurological deterioration. Although we tried to ensure not to miss a case of SICH by additionally checking medical discharge letters, under-reporting of SICH in total but also over-reporting, especially in the aspirin group, cannot be ruled out. Since local investigators were not masked to treatment allocation, there might also have been a lower threshold to undertake brain imaging in patients in the aspirin group and a tendency to attribute unrelated clinical deterioration to intracerebral haemorrhage. This factor might have increased the SICH rate in the aspirin group. A double-blinded placebo-controlled design would have prevented this bias, but high placebo production costs without obtained pharmaceutical support forced us to use a PROBE design. Although the SICH rate might be biased, the absolute number of SICHs in the aspirin group was still low and there is no need to change current practice to allow alteplase treatment in patients already on aspirin.26,27

Another limitation of the open-label design could have been that patients remembered their treatment allocation, and interpreted their outcomes more favourably in case of early treatment with aspirin. We consider this effect unlikely since the intervention consisted of only a single intravenous administration during an emergency treatment. Indeed, 70% of the patients did not recall, or incorrectly recalled treatment allocation making bias unlikely. The change in randomisation procedure is highly unlikely to induce selection bias because the treatment allocation difference of 29 patients was dispersed over 37 participating centres.

Our trial was done in a heterogeneous, acute stroke, population, because participating centres were located in both urban and rural areas and in academic and non-academic teaching hospitals as well as in non-teaching hospitals and resembles current acute stroke management. Because of this pragmatic design, our results have high external validity. The proportion of patients

### Table 3: Causes of poor outcome in patients with modified Rankin scale score of 3–6 at 3 months

<table>
<thead>
<tr>
<th>Cause</th>
<th>Aspirin (n=148)</th>
<th>Standard treatment (n=157)</th>
<th>Relative risk (95% CI)</th>
<th>p value*</th>
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<tr>
<td>Initial ischaemic stroke (including progressive stroke)</td>
<td>99 (66%)</td>
<td>102 (74%)</td>
<td>0 90 (0·77 to 1·04)</td>
<td>0·16</td>
<td>–7 6% (–18·1 to 3·0)</td>
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<td>Recurrent ischaemic stroke</td>
<td>10 (6·8%)</td>
<td>3 (2·2%)</td>
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<td>0·09</td>
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<td>Symptomatic intracranial haemorrhage</td>
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<td>Pre-existing poor functional status</td>
<td>17 (11·5%)</td>
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Panel: Research in context

Systematic review
We searched for reports published in Medline between Jan 1, 1950, and May 31, 2012, the Cochrane Central Register of Controlled Trials between Jan 1, 1993 and May 31, 2012, and Embase between Jan 1, 1988, and May 31, 2012, with the search terms “thrombolysis,” “antiplatelet therapy,” or “aspirin.” We restricted our search to English publications. We also hand searched bibliographies of relevant articles. There are no previous trials of early aspirin addition to intravenous alteplase in patients with acute ischaemic stroke. For patients with previous use of antiplatelet therapy, the National Institute of Neurological Disorders and Stroke trial showed less clinical deterioration associated with poor outcome after alteplase treatment.26 For patients with acute myocardial infarction, the combination of intravenous thrombolyis and aspirin substantially reduces mortality compared with thrombolyis alone.27 Most studies reporting on the combination of aspirin and alteplase in stroke are derived from observational thrombolyis registers presenting patients with previous use of aspirin or other antiplatelet agents. A cohort study of 301 patients showed that patients with previous use of antiplatelet therapy (mostly aspirin) before alteplase had a better outcome, despite an increased frequency of SICH.28 More recently, the large Safe Implementation of Thrombolysis in Stroke International Thrombolysis Register (SITS-ISTR) showed an absolute 1.4% increase of SICH in 11 865 patients with previous use of antiplatelet therapy with no clear effect on outcome.29

Interpretation
The results of this trial do not support a change of the current guidelines, which advise starting antiplatelet therapy 24 h after alteplase. With a favourable outcome in our trial differs substantially from the 37% reported in the recent and large third International Stroke Trial (IST-3).30 This finding can probably be explained by the quite different selection of patients included in both trials. Patients in IST-3 were older, had more severe symptoms, and were treated at patients included in both trials. Patients in IST-3 were from the 37% reported in the recent and large third treatment effect seems, therefore, very unlikely. However, with over 80% of the targeted patients included, a small non-significant trend towards a worse outcome in the treatment group occurred, and missing a beneficial treatment effect seems, therefore, very unlikely.

How should we proceed with treatment in view of the results of our trial? A beneficial effect of combining antiplatelet agents other than aspirin with alteplase seems unlikely since none of these combinations were associated with an improved outcome in the SITS-ISTR.31 Targeting patients with a high risk of reocclusion by advanced clot imaging techniques might be included in future studies. A challenge is to find new methods that safely increase the rate of reperfusion with stable recanalisation. A recent phase 2B trial with intravenous tenecteplase showed promising results with higher reperfusion rates in combination with better outcome compared with alteplase.32 If tenecteplase shows efficacy in a phase 3 trial, influence of previous use of aspirin and other antiplatelet agents will guide further research into the combination of tenecteplase and antiplatelet therapy. The results of our trial do not support a change of the current guidelines, which advise starting antiplatelet therapy 24 h after alteplase.

Contributors
SMZ contributed to study organisation, execution and statistical review, data analysis, data interpretation, and writing of the report. YBR contributed to funding, study conception, statistical design, data interpretation, review, and critique of the report. The steering committee contributed to review and critique of the report.

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Conflicts of interest
We declare that we have no conflicts of interest.

Acknowledgments
The trial was funded by a grant from the Dutch Heart Foundation (2005B118). We thank Simone Dierckx for coordinating the trial from January, 2007, to January, 2008; all patients, nurses, secretaries, neurologists, and residents who contributed to the ARTIS trial; and the research nurses Nadine Fleitour, Aniek Goriessen, and Mineke Ek for their administrative support and outcome assessment.

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