Optimizing thrombolysis in acute ischaemic stroke
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CHAPTER 3

EARLY ADMINISTRATION OF ASPIRIN IN PATIENTS TREATED WITH THROMBOLYSIS FOR ACUTE ISCHAEMIC STROKE: A RANDOMISED CONTROLLED TRIAL

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ABSTRACT

Background
Intravenous thrombolysis (IVT) is the only approved treatment for acute ischaemic stroke. After IVT-induced recanalisation, reocclusion is observed in 14–34% of the patients, probably because of platelet activation. Early administration of antiplatelet therapy after IVT may reduce the risk of reocclusion and improve outcome.

Methods
In this multicenter, randomised open-label trial with blind endpoint assessment, patients with acute ischaemic stroke treated with IVT were randomly assigned to 300 mg intravenous aspirin within 90 minutes after start of IVT or no additional treatment. In both treatment groups, oral antiplatelet therapy was started 24 hours after IVT. Primary endpoint was favourable outcome, defined as a score of 0–2 on the modified Rankin scale at 3 months. The occurrence of symptomatic intracranial haemorrhage (SICH) was a secondary endpoint. This trial was registered at the Netherlands Trial Register (NTR), number NTR822.

Results
The trial was terminated prematurely after inclusion of 642 (322 patients aspirin, 320 standard treatment) of a targeted 800 patients because of an excess of SICH and no indication of benefit in the aspirin group. At 3 months, 54.0% of the patients in the aspirin group versus 57.2% in the standard treatment group had a favourable outcome, absolute difference -3.2% (95% CI -10.8–4.2). Adjusted odds ratio was 0.91 (95% CI 0.66–1.26). SICH occurred more frequently in the aspirin group: 14 patients (4.3%) versus 5 (1.6%), absolute difference 2.8% (95% CI 0.2–5.4). SICH was more often the cause of poor outcome in the aspirin group (11 versus 1, p=0.006).

Conclusion
Early administration of aspirin in patients treated with IVT for acute ischaemic stroke does not improve outcome and increases the risk of SICH.
INTRODUCTION

Intravenous thrombolysis (IVT) with alteplase (or recombinant tissue plasminogen activator, rt-PA) is the only approved treatment for acute ischaemic stroke.\(^1,2\) After IVT, the overall recanalisation rate is 46\%.\(^3\) Reocclusion after initial recanalisation occurs in 14–34\% of the patients and is associated with clinical deterioration and poor outcome.\(^4-6\) Reocclusion has been attributed to increased platelet aggregation caused by the local thrombus, endothelial injury and probably the thrombolytic treatment itself.\(^7,8\) Antiplatelet therapy early after IVT may reduce the risk of reocclusion and thereby improve functional outcome. Indeed, prior use of antiplatelet therapy has been associated with higher rates of early recanalisation after IVT.\(^9\) In the National Institute of Neurological Disorders and Stroke trial, clinical deterioration associated with poor outcome was less frequent in patients with prior use of antiplatelet therapy.\(^10\) In patients with acute myocardial infarction, the combination of antiplatelet therapy and IVT reduces mortality considerably compared to IVT alone.\(^11\)

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

METHODS

Study design and patient population
ARTIS was a prospective, randomised, open-label clinical trial with blinded endpoint assessment (PROBE design). The rationale and the protocol of the study have been published before.\(^12,13\) The department of Neurology of the Academic Medical Center, University of Amsterdam (AMC) designed and coordinated the trial. Thirty-seven centres across the Netherlands participated (3 academic hospitals, 20 non-academic teaching hospitals and 14 non-teaching hospitals: see end of this chapter). Only centres with an annual IVT rate above 20 could participate.
Patients were eligible if they were ≥18 years and were treated with IVT for acute ischaemic stroke. Patients who had used antiplatelet therapy in the last five days prior to the stroke were excluded. Other exclusion criteria were known thrombocytopenia at presentation or a thrombocyte count ≤100 *10^9/l, contraindications to aspirin, anticoagulant therapy in the last five days and legal incompetence prior to 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 carried out according to Good Clinical Practice standards, and was independently monitored by the Clinical Research Unit of the AMC. The trial was registered at 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 IVT (<2 hours, 2–3 hours, >3 hours), and centre using permuted blocks within strata. Due to large imbalances in treatment allocation because of an unexpected high number of participating centres, centre was removed as stratification factor after inclusion of 465 patients (218 in the aspirin group versus 247 in the standard treatment group), and the randomisation method was changed into a (non-deterministic) minimization method balancing on age, sex and time between symptoms and start of IVT.14 Local investigators and patients were not blinded, but the research nurses who performed the follow-up interviews were blinded to treatment allocation.

Study procedures
Patients were assigned, in a 1:1 ratio, to 300 mg intravenous aspirin (lysine acetyl-salicylate, Aspégic, Sanofi-Aventis, the Netherlands) within 90 minutes after the start of IVT or to standard treatment with IVT alone. Intravenous instead of regular oral administration was chosen to prevent exclusion of patients with dysphagia and to guarantee faster uptake.35 Intravenous aspirin was supplied by local hospital pharmacies. In both treatment groups, IVT with alteplase 0.9 mg/kg was administered within 4.5 hours after symptom onset and oral antiplatelet ther-
apy was initiated 24 hours after IVT according to international guidelines.\textsuperscript{16,17} Demographic and clinical characteristics were collected 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)\textsuperscript{18} at baseline and at 7–10 days (or at discharge if earlier). In all patients, a cranial CT scan was performed before the start of IVT. In case of neurological deterioration, defined as an increase of ≥4 points 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 blinded research nurses assessed functional outcome at 3 months with a structured telephone interview.\textsuperscript{19} 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.

Endpoints
The primary endpoint was favourable outcome at 3 months, defined as being independent (mRs 0–2), in accordance to the Cochrane analysis of thrombolysis in stroke.\textsuperscript{20} 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 increase on the NIHSS in combination with intracranial haemorrhage on follow-up CT scan without other obvious causes for the deterioration. All locally reported SICH were centrally reviewed by the outcome evaluation committee, consisting of two neurologists, of which one was blinded, who had access to medical discharge letters and cranial CT scans. Severe systemic bleeding was defined as a 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 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 the outcome evaluation committee. In case of discrepancy between the judgments of the two neurologists, a third blinded neurologist was consulted. In patients with severe (progressive) stroke without any recovery, the cause of poor outcome was considered to be the initial ischaemic stroke. Patients with an mRs score ≥3 due to permanent disability at time of randomisation were classified as pre-existing poor functional status, regardless of the further course during hospitalization.

Safety
In addition to SICH and severe systemic bleeding, serious adverse events (SAEs) were defined as any event that resulted in death, was life threatening at the time of the event, required hospitalization or prolongation of hospitalization, or resulted in persistent or significant disability or incapacity. The data and safety monitoring board (DSMB) was instantly informed about all SAEs in both treatment groups. Discharge letters were additionally screened for haemorrhagic complications at the coordinating center. The DSMB could advise the steering committee to stop the trial in case of safety concerns without pre-specified stopping boundaries.

Besides safety monitoring a planned interim analysis for efficacy was performed after follow-up assessment of the first 400 patients. In the DSMB charter, as predefined stopping rule for futility was formalized using 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.

Sample size and statistical analysis
A 10% absolute increase in favourable outcome was considered clinically relevant. Based on the results of a Cochrane analysis and unpublished results from our own institution, we assumed that 50% of patients would have a favourable outcome. Four hundred patients per group (total 800 patients) were required to have a 80% power with a two-sided significance level of 0.05 to detect a 10% increase in favourable outcome.
Analyses were based on the intention-to-treat principle. Baseline characteristics and outcome parameters were summarized using 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 / percentages with its 95% confidence interval (CI). We additionally adjusted the primary outcome for clinically relevant baseline imbalances and factors used as stratifying variable during randomisation with multivariate logistic regression (adjusted odds ratio). Patients with mRs ≤2 before stroke were analysed separately in a post-hoc analysis. The differences between treatment groups with regard to the secondary outcomes were analysed, using χ², Fisher’s exact or Mann Whitney U tests, where appropriate. P-values <0.05 were considered statistically significant.

For the safety analysis, all SAEs were additionally analysed per-protocol in patients who actually received 300 mg intravenous aspirin within 90 minutes after start of IVT and in patients who received no intravenous aspirin.

ROLE OF THE FUNDING SOURCE

The sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to data in the study and final responsibility to submit for publication.

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. At that time, inclusion was prematurely halted at 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 implications of this increased SICH rate, the results on the primary endpoint were revealed to the DSMB. Based on the primary endpoint results of 564 patients, the DSMB recommended the steer-
Figure 3.1: Study profile

...ing committee to stop the trial because there was no prospect of benefit in the aspirin group (futility). The steering committee concluded that although there was no significant overall worse outcome, continuation of the trial was highly unlikely to result in benefit for the patients and therefore adopted the DSMB advice. Patient enrollment was stopped on May 20, 2011.

In total, 322 patients were assigned to early aspirin and 320 to standard treatment (Figure 3.1). There were 34 (10.6%) protocol violations in the aspirin group with most (22 [65%]) caused by a delay of aspirin administration (median delay 17 minutes). Baseline characteristics are summarized in Table 3.1. Age, sex, independence prior to stroke, stroke severity, and number of patients per centre type (academic, teaching hospital, and non-teaching hospital) were equally distributed between treatment groups. In the aspirin group, slightly more patients had hypertension, diabetes, or previous stroke compared to the standard treatment
Early administration of aspirin: a randomised controlled trial

Table 3.1: Demographic and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Aspirin (n=322)</th>
<th>Standard treatment (n=320)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.1 (13.8)</td>
<td>66.7 (13.5)</td>
</tr>
<tr>
<td>Men</td>
<td>163 (50.6)</td>
<td>160 (50.0)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>309 (96.0)</td>
<td>310 (96.9)</td>
</tr>
<tr>
<td>MRs 0–2 before stroke</td>
<td>303 (94.1)</td>
<td>299 (93.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>140 (43.5)</td>
<td>125 (40.3)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>38 (11.8)</td>
<td>26 (8.1)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>36 (11.2)</td>
<td>35 (10.9)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>11 (3.4)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Previous intracranial haemorrhage</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>9 (5–15)</td>
<td>9 (5–14)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>155.6 (22.4)</td>
<td>156.5 (21.6)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>83.4 (13.1)</td>
<td>84.5 (14.0)</td>
</tr>
<tr>
<td>Time between onset and IVT (minutes)</td>
<td>124.3 (54.4)</td>
<td>127.9 (57.6)</td>
</tr>
<tr>
<td>Time between IVT and aspirin (minutes)</td>
<td>67.0 (25.4)</td>
<td>-</td>
</tr>
<tr>
<td>Centre type (number of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic hospital</td>
<td>60 (18.6)</td>
<td>64 (20.0)</td>
</tr>
<tr>
<td>Teaching hospital</td>
<td>177 (55.0)</td>
<td>180 (56.3)</td>
</tr>
<tr>
<td>Non-teaching hospital</td>
<td>85 (26.4)</td>
<td>76 (23.8)</td>
</tr>
</tbody>
</table>

Data are number (%), mean (standard deviation), or median (interquartile range).

MRs indicates modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; IVT, intravenous thrombolysis.

Study medication was administered at an average of 67 minutes after start of IVT.

At 3 months, the primary outcome was not different between groups: 54.0% (174 patients) in the aspirin group compared to 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, 95% CI 0.82–1.09, OR 0.88, 95% CI 0.64–1.22, p=0.42, Figure 3.2). 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 (95% CI 0.66–1.26). In patients with mRs score ≤2 before stroke (602 patients), adjusted OR was 0.88 (95% CI 0.63–1.22).

Mortality was 11.2% (36 patients) in the aspirin group compared to 9.7% (31 patients) in the standard treatment group (p=0.54). Among the survivors (mRs 0–5), Mann Whitney U analysis showed no different mRs scores between groups (p=0.86, Figure 3.2). Incorporating deaths as mRs 5 revealed the same results (p=0.85). At 7–10 days after baseline, neurological deficit of patients was sim-
ilar in both groups: median NIHSS 2 (interquartile range [IQR] 0–7) in the aspirin group and 3 (IQR 1–7) in the standard treatment group (p=0.11).

In total, 61 patients (18.9%) in the aspirin group had 65 SAEs whereas 43 patients (13.4%) in the standard treatment group had 50 SAEs (Table 3.2). In the per-protocol analysis, 290 patients in the aspirin group and 325 in the standard treatment group were included (Figure 3.1). Per-protocol analysis showed that 56 aspirin treated patients (19.3%) reported a total of 60 SAEs compared to 44 standard treatment patients (13.5%) reporting 51 SAEs.

In the aspirin group, 14 patients had SICH (4.3%) compared to 5 (1.6%) in the standard treatment group (absolute difference 2.8% 95% CI 0.2–5.4; RR 2.78, 95% CI 1.01–7.63; OR 2.86, 95%CI 1.02–8.05, p=0.04); absolute difference in the per-protocol analysis was 3.3%, 95% CI 0.5–6.1; RR 3.14, 95% CI 1.14–8.61; OR 3.25, 95% CI 1.08–10.45, p=0.02. Most of the SICH in both groups occurred within 36 hours (12 in the aspirin and four in the standard treatment group). None of the patients with SICH had their diagnosis changed into another diagnosis after central review. Severe systemic bleeding occurred in one patient in the aspirin group and in two in the standard treatment group.

The causes of poor outcome are listed in Table 3.3. Initial stroke was the main cause of poor outcome in both treatment groups. SICH was more often the cause of poor outcome in the aspirin group compared to the standard treatment group (7.4% versus 0.7%, p=0.006). Of the 14 patients with SICH in the aspirin group
### Table 3.2: Serious adverse events

<table>
<thead>
<tr>
<th></th>
<th>Intention-to-treat</th>
<th>Per-protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin (n=322)</td>
<td>Standard treatment (n=320)</td>
</tr>
<tr>
<td>Total number of patients with SAE</td>
<td>61</td>
<td>43</td>
</tr>
<tr>
<td>Total number of SAEs</td>
<td>65</td>
<td>50</td>
</tr>
<tr>
<td>SICH</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Other ICH</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td>Serious systemic bleeding</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other systemic bleeding</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Progressive ischaemic stroke</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Seizure</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

* This patient was re-admitted 5 weeks after IVT because of an ICH with an increase of <2 points on the National Institutes of Health Stroke Scale.

SAE indicates serious adverse event; SICH, symptomatic intracranial haemorrhage; ICH, intracranial haemorrhage.

(Table 3.2), 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 3.2), 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 intracranial haemorrhage.

After the outcome assessment interview, recall of treatment allocation was asked in 482 patients (75%). 339 (70%) of the patients / caregivers did not remember the treatment or made a wrong allocation choice.

**DISCUSSION**

The current study shows that intravenous administration of 300 mg aspirin within 90 minutes after start of IVT does not improve functional outcome at 3 months but increases the risk of SICH.
Table 3.3: Causes of poor outcome in patients with modified Rankin scale score of 3–6 at 3 months

<table>
<thead>
<tr>
<th>Cause of poor outcome</th>
<th>Aspirin (n=148)</th>
<th>Standard treatment (n=137)</th>
<th>Relative risk (95% CI)</th>
<th>p*</th>
<th>Absolute difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial ischaemic stroke (including progressive stroke)</td>
<td>99 (66.9)</td>
<td>102 (74.5)</td>
<td>0.90 (0.77–1.04)</td>
<td>0.16</td>
<td>-7.6 (-18.1–3.0)</td>
</tr>
<tr>
<td>Recurrent ischaemic stroke</td>
<td>10 (6.8)</td>
<td>3 (2.2)</td>
<td>3.09 (0.87–10.89)</td>
<td>0.09</td>
<td>4.6 (-0.2–9.3)</td>
</tr>
<tr>
<td>Symptomatic intracranial haemorrhage</td>
<td>11 (7.4)</td>
<td>1 (0.7)</td>
<td>10.18 (1.33–77.83)</td>
<td>0.006</td>
<td>6.7 (2.2–11.2)</td>
</tr>
<tr>
<td>Other cerebral pathology</td>
<td>2 (1.4)</td>
<td>4 (2.9)</td>
<td>0.46 (0.09–2.49)</td>
<td>0.43</td>
<td>-1.6 (-5.0–1.8)</td>
</tr>
<tr>
<td>Systemic ischaemic disease (including myocardial infarction)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Systemic haemorrhage</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>0.93 (0.06–14.66)</td>
<td>1.0</td>
<td>-0.1 (-2.0–1.9)</td>
</tr>
<tr>
<td>Other systemic pathology</td>
<td>8 (5.4)</td>
<td>5 (3.6)</td>
<td>1.48 (0.50–4.42)</td>
<td>0.48</td>
<td>1.8 (3.1–6.6)</td>
</tr>
<tr>
<td>Pre-existing poor functional status</td>
<td>17 (11.5)</td>
<td>21 (15.3)</td>
<td>0.75 (0.41–1.36)</td>
<td>0.34</td>
<td>3.9 (-11.8–4.1)</td>
</tr>
</tbody>
</table>

Data are number (%) unless stated otherwise.

* χ² test or Fisher’s exact test, where appropriate.

CI indicates confidence interval.

A previous trial investigated the effect of combining aspirin (300 mg oral or 100 mg intravenous in case of swallowing difficulties) with IVT using streptokinase instead of alteplase. This Multicenter Acute Stroke Trial-Italy study showed that the combination of early administration of aspirin and streptokinase increased the 10-day case fatality rate, mainly due to a high SICH rate of 10%.22 However, of the patients who survived the number of patients with favourable outcome (mRs score 0–2) was higher (65%) in the combination group compared to the streptokinase only group (53%). Because the rate of SICH with alteplase is lower than with streptokinase,20 we assumed when we started our trial that the benefits of early administration of aspirin would outweigh the risks. Indeed, a cohort study showed that patients with prior use of antiplatelet therapy (mostly aspirin) before alteplase had indeed a better outcome, despite an increased frequency of SICH.23 However, our trial results show otherwise. As we now know, our findings are in line with results from the large observational Safe Implementation of Thrombolysis in Stroke International Thrombolysis Register (SITS-ISTR) that showed an absolute 1.4% increase of SICH in patients with prior use of antiplatelet therapy with no clear effect on outcome.24
The increased risk of SICH in the patients treated with early aspirin has to be interpreted with caution since the effect relies on a relative small number of patients and a very low SICH rate in the standard treatment group. The rate of SICH in the aspirin group is still within the range of 2.4–8.9% reported in other IVT trials.\textsuperscript{1,2,25–27} Comparisons with these other trials are however limited by the different definitions of SICH used in these trials. Our SICH definition is similar to the definition used in the European Cooperative Acute Stroke Study III which reported a rate of 2.4%.\textsuperscript{26}

In contrast to the IVT trials which required follow-up imaging in each patient, our low-budget and pragmatic designed trial requested only follow-up CT in case of neurological deterioration. Although we tried to ensure not to miss a 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 ICH. This 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 IVT in patients already on aspirin.\textsuperscript{16,17}

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 unlikely since the intervention consisted of only a single intravenous administration during an emergency treatment. Indeed, 70% of the patients did not, or incorrectly, recall treatment allocation making bias unlikely. It is highly unlikely that the randomisation procedure change induced selection bias as the treatment allocation difference of 29 patients was dispersed over 37 participating centres.

Our trial was performed 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, we consider our results of high external validity. The proportion of patients with favourable outcome in our trial differs considerably from the 37% reported in the recent and large third International Stroke Trial (IST-3). This 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 later time points.

Premature termination of our trial has probably reduced the precision of the outcome assessment. In the absence of a significant difference between the groups, the estimated treatment effect can be underestimated and important treatment effects may potentially be missed. Moreover, in our study, the sample size calculation was based on the former 3 hours-time window instead of the current 4.5 hours, which might have weakened the power of our study. However, with over 80% of the targeted patients included, there was a small trend towards a worse outcome in the treatment group, and missing a beneficial treatment effect seems therefore very unlikely.

How should we have to proceed after this trial? A beneficial effect of combining other antiplatelet agents than aspirin with IVT seems unlikely since none of these combinations were associated with an improved outcome in the SITS-ISTR. Targeting patients with a higher risk of reocclusion by advanced clot imaging techniques might be included in future studies. A challenge is to find new methods that increase safely 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 to alteplase. If tenecteplase will show efficacy in a phase 3 trial, influence of prior use of aspirin and other antiplatelet agents will guide further research into the combination of tenecteplase and antiplatelet therapy.

In conclusion, early administration of aspirin after IVT in patients with acute ischaemic stroke does not improve functional outcome at 3 months. There was an increased risk of SICH in the aspirin group although the trial design cannot rule out a potential SICH over-reporting in the aspirin group. The results of this trial do
not support a change of the current guidelines, which advise to start antiplatelet therapy 24 hours after IVT.

ACKNOWLEDGMENTS

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