Outcome and Symptomatic Bleeding Complications of Intravenous Thrombolysis Within 6 Hours in MRI-Selected Stroke Patients

Comparison of a German Multicenter Study With the Pooled Data of ATLANTIS, ECASS, and NINDS tPA Trials

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Background and Purpose—We compared outcome and symptomatic bleeding complications of intravenous tissue plasminogen activator (IV-tPA) within 6 hours of symptom onset in MRI-selected patients with acute middle cerebral artery infarction with the pooled data of the large stroke tPA trials.

Methods—Patients were examined by perfusion-weighted and diffusion-weighted imaging within 6 hours. Within 3 hours, patients were treated according to Second European-Australasian Acute Stroke Study (ECASS II) criteria. After 3 to 6 hours, treatment with IV-tPA was performed based on MRI findings. Favorable outcome was assessed after 90 days using a dichotomized modified Rankin scale score of 0 to 1. Intracerebral bleeding complications were assessed on follow-up MRI or computed tomography. Data were compared with the pooled placebo and pooled tPA patients of the ATLANTIS, ECASS, and National Institute of Neurological Disorders and Stroke (NINDS) tPA trials.

Results—From 174 MRI-selected tPA patients, 62% (n=108) were treated in ≤3 hours and 38% (n=66) after 3 to 6 hours. Favorable outcome was more frequent in MRI-selected tPA patients (48% [95% CI, 39 to 54]) compared with pooled placebo (33% [95% CI, 31 to 36]; P<0.001) and pooled tPA patients (40% [95% CI, 37 to 42]; P=0.046). Odd ratios for favorable outcome in the MRI-selected tPA group were 1.82 (1.32 to 2.51) compared with the pooled placebo group and 1.39 (1.01 to 1.92) compared with the pooled tPA group. The rate of symptomatic intracerebral hemorrhage in MRI-selected tPA patients (3% [95% CI, 0 to 5]) was lower than in the pooled tPA group (8% [95% CI, 7 to 10]; P=0.012) and comparable to the pooled placebo group (2% [95% CI, 1 to 3]; P=0.392).

Conclusions—This study supports that it is safe and effective to expand the time window for IV-tPA up to 6 hours in patients with tissue at risk as defined by MRI. (Stroke. 2006;37:852-858.)

Key Words: magnetic resonance imaging, diffusion-weighted magnetic resonance imaging, perfusion-weighted outcome stroke, acute thrombolytic therapy, tissue plasminogen activator

Intravenous thrombolysis with intravenous tissue plasminogen activator (IV-tPA) within 3 hours of symptom onset significantly improves clinical outcome in acute ischemic stroke (AIS). However, the strict 3-hour time window represents a major obstacle for the use of IV-tPA. Three multicenter randomized placebo-controlled trials tested the benefit of IV-tPA given within 6 hours of stroke onset and failed to demonstrate a beneficial effect on primary end points. The pooled analysis of the tPA stroke trials showed a potential benefit of tPA beyond the
3-hour time window, which, however, appeared not to extend to the full 6 hours.7

Multiparametric MRI is discussed as a tool for the selection of potential tPA-responsive patients beyond the 3-hour time window.8–11 Perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) can be used to operationally define tissue at risk of infarction being characterized by a PWI/DWI mismatch.11–13 It is assumed that timely reperfusion may prevent this tissue from infarction even beyond 3 hours after symptom onset.

In our study, we used MRI to select patients for IV thrombolysis within an expanded time window of 6 hours and studied outcome and symptomatic intracerebral bleeding complications in these patients in comparison with data from the large clinical trials of IV-tPA in acute stroke.

Materials and Methods

Study Concept

In 1999, the MRI in Acute Stroke Study Group of the “German Competence Network Stroke” started a prospective study in which MRI, according to a standardized protocol, was used as a tool to select patients for treatment with IV-tPA within an expanded time window of up to 6 hours.

Patients

Three stroke centers contributed data to this study (university hospitals in Hamburg, Heidelberg, and Cologne). During different time periods between 1999 and 2003, all AIS patients presenting within 6 hours of symptom onset were examined by MRI (except for those with contraindications against MRI). Only patients with a complete stroke MRI study, including PWI and DWI, were included in this study. Patients enrolled in clinical trials of thrombolytics or neuroprotectives were excluded from the analysis.

Treatment

IV thrombolysis was performed ≤3 hours according to Second European-Australasian Acute Stroke Study (ECASS II) criteria.6 In patients for whom MRI was the primary imaging modality, modified criteria were used. Patients with signs of intracerebral hemorrhage on MRI and those with large DWI lesions (exceeding 50% of the middle cerebral artery territory) were excluded from thrombolysis. After 3 to 6 hours, IV thrombolysis was performed as an individual decision based on MRI findings after informed consent according to the Declaration of Helsinki. For the decision whether to treat or not, PWI and DWI lesion volumes were assessed at the scanner by the neuroradiologist and neurologist on duty without any further post-processing. In general, patients with signs of intracerebral hemorrhage, large DWI lesions, and without a relevant amount of PWI/DWI mismatch were excluded from thrombolysis. The study was approved by the local institutional review boards in all participating centers.

Clinical Assessment

Severity of neurological deficit at admission was assessed using the National Institutes of Health Stroke Scale (NIHSS).15 Outcome was assessed 90 days after stroke using the modified Rankin Scale (mRS).15 Favorable outcome was defined as a score of ≤1 on the mRS according to primary end points used in the National Institute of Neurological Disorders and Stroke (NINDS)1 and ECASS II trials.6 All clinical assessments were made by experienced neurologists blinded to the imaging data. According to the definitions used in the ECASS trials,6 symptomatic intracerebral hemorrhage (SICH) was defined as any signs of hemorrhage on follow-up computed tomography (CT) or MRI associated with clinical deterioration of ≥4 points on the NIHSS.

MRI Protocol

MRI studies were performed on 1.5-T clinical whole body scanners with echo planar capabilities (Magnetom Symphony; Siemens; Marconi Edge; Philips Intera). All centers performed acute stroke MRI protocols including an axial DWI sequence, a PWI sequence, a time-of-flight magnetic resonance angiography of the intracranial arteries, a T2-

| TABLE 1. Characteristics of MRI-Selected tPA Patients 0–3 Hours vs 3–6 Hours |
|---------------------------------|----------------|----------------|
| tPA 0–3 h (n=108) | tPA 3–6 h (n=66) | Group Comparison |
| Age (y), median (range) | 64 (35–86) | 64 (27–91) | 0.839* |
| Sex: female, n (%) | 47 (43.5) | 23 (34.8) | 0.270† |
| Side of infarction: left middle cerebral artery, n (%) | 72 (66.7) | 46 (69.7) | 0.867† |
| NIHSS at admission, median (range) | 13 (0–23) | 13 (3–42) | 0.501* |
| Onset to MRI time (min), median (range)** | 117 (48–270) | 205 (120–345) | n.a. |
| OTT (min), median (range)** | 135 (45–180) | 225 (185–360) | n.a. |
| MRI lesion volumes | | | |
| DWI lesion (mL), median (range) | 14.2 (0.0–187.0) | 18.3 (0.5–158.0) | 0.142* |
| PWI lesion (mL), median (range) | 95.0 (0.0–673.0) | 132.9 (0.0–505.0) | 0.039* |
| PWI/DWI mismatch ratio, median (range) | 4.0 (0.0–940.0) | 5.6 (0.0–47.3) | 0.417* |
| PWI/DWI mismatch volume, median (range) | 72.5 (–11.0–609.8) | 108.6 (–18.6–399.0) | 0.020* |
| PDI/DWI mismatch ratio ≤1.2, n (%) | 20 (18.5) | 6 (9.1) | 0.125† |
| PDI/DWI mismatch ratio >1.2, n (%) | 88 (81.5) | 60 (90.9) | 0.125† |
| Outcome parameters (day 90) | | | |
| mRS, median (range) | 2 (0–6) | 2 (0–6) | 0.590* |
| Favorable outcome (mRS 0–1), n (%) | 50 (46.3) | 33 (50.0) | 0.643† |
| Dead, n (%) | 9 (8.3) | 4 (6.1) | 0.769† |
| SICH, n (%) | 3 (2.8) | 2 (3.0) | 1.000† |

*Mann–Whitney U test; †2-tailed Fisher exact test; **exact OTT missing for 14 patients between 0 and 3 hours and 9 patients between 3 and 6 hours; n.a. indicates not applicable.
weighted sequence and a T2*-weighted sequence for the exclusion of intracranial hemorrhage. The scanning time was <20 minutes. Sequence parameters for this standardized protocol have been described recently.16

MRI Lesion Volume Measurement
Postprocessing of the PWI and DWI image data were performed offline in each participating center with locally established software. Details of the postprocessing procedures in the different centers have been published previously.17–20 In short, DWI lesion volumes were delineated either on apparent diffusion coefficient (ADC) maps or on diffusion-weighted (b=1000) images using standardized ADC thresholds or standardized window settings for manually tracing the lesion. For the PWI images, maps of the time to peak or of the mean transit time were calculated, and standardized window settings or thresholds were used to delineate the perfusion lesion.

Pooled Data of ATLANTIS, ECASS, and NINDS Trials
Recently, a pooled analysis of the data of the clinical stroke tPA trials (ATLANTIS, ECASS, and NINDS) has been published.3 For the present analysis, we excluded ECASS I data because of the different tPA dose of 1.1 mg/kg body weight used in this trial compared with 0.9 mg/kg used in the other trials and in our study. Data on baseline characteristics, outcome, and hemorrhagic transformation from the 5 remaining trials were extracted and pooled for both placebo and tPA patients (Table 1). These groups are further referred to as pooled placebo and pooled tPA group.

Statistical Analysis
All values are presented as median (range) for continuous variables and counts (percentage) for categorical variables. CIs and odds ratios (OR) were calculated. Group comparisons were made using the Mann–Whitney U test for continuous variables and Fisher exact test for categorical variables (SPSS 9.0.1; SPSS Inc).

Results
Characteristics of MRI-Selected tPA Patients
From 174 MRI-selected tPA patients, 62% (n=108) were treated ≤3 hours and 38% (n=66) after 3 to 6 hours (Table 1). Patients treated within 3 hours, and those after 3 to 6 hours did not differ regarding baseline characteristics, MRI lesion volumes, and outcome parameters. The majority of patients (n=148; 85%) presented with a PWI/DWI mismatch ratio >1.2. The frequency of SICH was comparable in both groups.

Group Comparison: Baseline Characteristics
MRI-selected tPA, pooled placebo, and pooled tPA patients were similar regarding sex and NIHSS on admission (Table 2)

<table>
<thead>
<tr>
<th></th>
<th>Pooled Placebo</th>
<th>Pooled tPA</th>
<th>MRI Selected tPA</th>
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<tr>
<td>0–6 h</td>
<td>n=1081</td>
<td>n=1085</td>
<td>n=174</td>
</tr>
<tr>
<td>Age (y), median (range; 95% CI)</td>
<td>68.0 (18–101)</td>
<td>69.0 (25–98)</td>
<td>62.0 (27–89)</td>
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<tr>
<td>Sex: female, n (%; 95% CI)</td>
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<td>448 (41.3)</td>
<td>70 (40.2)</td>
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<td>NIHSS on admission, median (range; 95% CI)</td>
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<td>11.0 (1–42)</td>
<td>13.0 (0–42)</td>
</tr>
<tr>
<td>OTT (min), median (range; 95% CI)*</td>
<td>230 (54–360)</td>
<td>235 (65–365)</td>
<td>165 (45–360)</td>
</tr>
<tr>
<td>3–6 h</td>
<td>n=427</td>
<td>n=416</td>
<td>n=108</td>
</tr>
<tr>
<td>Age (y), median (range; 95% CI)</td>
<td>67.1 (26–101)</td>
<td>69.4 (31–98)</td>
<td>62.0 (35–82)</td>
</tr>
<tr>
<td>Sex: female, n (%; 95% CI)</td>
<td>173 (40.5)</td>
<td>172 (41.3)</td>
<td>47 (43.5)</td>
</tr>
<tr>
<td>NIHSS on admission, median (range; 95% CI)</td>
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<td>13.0 (1–42)</td>
<td>13.0 (0–23)</td>
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<tr>
<td>OTT (minutes), median (range; 95% CI)*</td>
<td>135 (54–180)</td>
<td>135 (65–195)</td>
<td>135 (45–180)</td>
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<tr>
<td>3–6 h</td>
<td>n=654</td>
<td>n=669</td>
<td>n=66</td>
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<tr>
<td>Age (y), median (range; 95% CI)</td>
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<td>68.0 (25–84)</td>
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</tr>
<tr>
<td>Sex: female, n (%; 95% CI)</td>
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<td>276 (41.3)</td>
<td>23 (34.8)</td>
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<td>NIHSS on admission, median (range; 95% CI)</td>
<td>10.0 (3–42)</td>
<td>10.0 (2–30)</td>
<td>14.0 (3–42)</td>
</tr>
<tr>
<td>OTT (minutes), median (range; 95% CI)*</td>
<td>279 (185–360)</td>
<td>281 (183–365)</td>
<td>225 (185–360)</td>
</tr>
</tbody>
</table>

95% CIs are given for mean values (continuous) and percent (categorical).
*Exact OTT missing for 14 patients between 0 and 3 hours and 9 patients between 3 and 6 hours in the MRI-selected tPA group.
2). MRI-selected tPA patients were younger (62 years) than pooled placebo (68 years) and pooled tPA patients (69 years). Median onset to treatment time (OTT) was lower for MRI-selected tPA patients (165 minutes) compared with pooled placebo (230 minutes) and pooled tPA patients (235 minutes).

**Group Comparison: Favorable Outcome**

Outcome measurements are given in Table 3 and Figure 1. Compared with the pooled placebo group (33.4%), the number of patients with a favorable outcome was higher in MRI-selected tPA patients (47.4%), with an absolute increase...
of 14.3% and a relative increase of 42.8% in the number of patients with a favorable outcome. This results in a number needed to treat (NNT) of 7. Compared with the pooled tPA group (39.6%), a higher percentage of MRI-selected tPA patients (47.4%) reached a favorable outcome, representing an absolute increase of 8.1% and a relative increase of 20.5% in the number of patients with a favorable outcome. This translates into an NNT of 12.

Patients in the MRI-selected tPA group were more likely to reach a favorable outcome than both pooled placebo and pooled tPA patients (odds ratios, 1.82 [1.32 to 2.51] and 1.39 [1.01 to 1.92]; Figure 2A).

**Group Comparison: Mortality, SICH**

Mortality rates were lower in the MRI-selected tPA group (7.5%) compared with both the pooled tPA (13.4%) and (as a trend) to the pooled placebo group (12.1%) (Table 3). Odds ratios show that death after 90 days was less likely in MRI-selected tPA patients compared with pooled placebo or pooled tPA patients (odds ratio, 0.59 [0.32 to 1.09] and 0.52 [0.29 to 0.95]; Figure 2B). The rate of SICH in MRI-selected tPA patients (3.0%) was comparable to that in the pooled placebo group (2.1%) and lower than in the pooled tPA group (8.45%).

**Discussion**

Since the approval of IV-tPA for the treatment of AIS within 3 hours of symptom onset, the time window for thrombolysis has been a matter of controversy. There is no pathophysiological basis for a restriction of the therapeutic time window to 3 hours, and several case series have shown that

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Odds ratio for a favorable outcome (A) and death (B) at 3 months after stroke. Favorable outcome was defined as mRS score of 0 to 1 at day 90. Odds ratios are given for the whole group (0 to 6 hours) and for subgroups defined by OTT (0 to 3 hours, 3 to 6 hours).
patients may benefit from intravenous thrombolysis beyond the 3-hour time window.\textsuperscript{10,19,21–25}

In our study, the number of patients with a favorable outcome was higher in MRI-selected tPA patients than in both pooled placebo and pooled tPA patients from the large clinical tPA stroke trials. In the pooled data from the large tPA stroke trials, the tPA treatment effect accounts for an absolute increase in favorable outcome of 6.2\% within 6 hours. Compared with these data, the extra effect of using MRI for patient selection appears quite remarkable, with an absolute increase of favorable outcome of 8.1\% (NNT 12) compared with unselected tPA patients and of 14.3\% (NNT 7) compared with placebo. In other words, if MRI is used to identify patients for treatment with IV-tPA ≤6 hours, 8 of 100 patients will additionally reach a favorable outcome compared with treatment of patients selected by clinical criteria and CT. Moreover, in MRI-selected tPA patients, mortality was lower than in both the placebo and the treatment groups from the pooled tPA trials. Finally, in our group of MRI-selected patients, the rate of SICH was lower than in the treatment group of the large stroke tPA trials.

We found no difference in outcome or symptomatic intracerebral bleeding complications within the group of MRI-selected tPA patients between patients treated within 3 hours and those treated after 3 to 6 hours. Similar results (ie, a comparable outcome for patients treated in ≤3 hours and after 3 to 6 hours) have been reported by 2 previous studies.\textsuperscript{10,25} This result is especially intriguing because in the pooled analysis of the clinical tPA trials, outcome was found to be strongly associated with OTT.\textsuperscript{7} Obviously, this clear association does not apply if patients are selected by MRI. This is in parallel to findings in the recently published phase II Desmoteplase in Acute Ischemic Stroke (DIAS) trial, in which OTT was not indicative of clinical outcome in a sample of MRI-selected patients.\textsuperscript{26}

How can this discrepancy regarding the association between OTT and clinical outcome be explained? A number of MRI studies have shown that a high percentage of AIS patients has penumbral patterns beyond the first 3 hours.\textsuperscript{10,17,19,21–24,27} The percentage of patients with a mismatch pattern continuously decreases over time, from ≈100\% ≤3 hours to 4 of 9 patients (44\%) after 18 to 24 hours in a previous report.\textsuperscript{27} In an unselected sample, the number of patients likely to benefit from thrombolysis will therefore wane over time, and the overall treatment effect will decline.\textsuperscript{7} On the other hand, patients with penumbral patterns on MRI may benefit independent of time from symptom onset, although it will become more difficult to find relevant numbers of these patients as time passes by.

There are several possible explanations for the better outcome in the group of MRI-selected tPA patients. From a pathophysiological perspective, patients with penumbral patterns are more likely to benefit from recanalization therapy, and it was hypothesized that MRI allows the identification of patients with tissue at risk of infarction, that are suitable for thrombolysis. Indeed the majority of patients in the MRI-selected group presented with a PWI/DWI mismatch pattern (85\%). Apart from mismatch, one might also speculate that the exclusion of patients with large DWI lesions from thrombolysis might play a major role. MRI has been found to be more sensitive in the detection of early ischemic signs than CT,\textsuperscript{28} and large early ischemic lesions were found to be associated with a higher incidence of SICH and a worse outcome.\textsuperscript{29} The small number of symptomatic intracerebral bleeding complications in our sample of MRI-selected patients may be a reflection of this selection effect.

The fear of an increased risk of intracerebral hemorrhage represents a frequent concern against an expansion of the time window for thrombolysis. However, in the pooled analysis of the large tPA stroke trials, hemorrhage was not associated with OTT.\textsuperscript{7} In line with this, neither in our study nor in a further report of IV-tPA in ≤6 hours\textsuperscript{25} or in the DIAS trial,\textsuperscript{26} OTT did interact with the frequency of severe intracerebral hemorrhage.

There are limitations to our study. In the absence of a randomized control group of AIS patients, we used the largest available data set of AIS patients ≤6 hours (ie, the data from the large stroke tPA trials) as a control group for our analysis. Therefore, group comparisons have to be interpreted with caution. Use of MRI as selection tool and inclusion criterion might introduce a certain bias because we do not know how many patients dropped out of the study because of 1 of the following reasons: unavailability of the MRI scanner, unstable clinical condition, or contraindications against MRI. Moreover, there was a difference between the group of MRI-selected tPA patients and pooled patients from the tPA trials regarding OTT within the 3- to 6-hour time window. There was a further imbalance regarding age, with MRI-selected tPA patients being slightly younger than patients in the large clinical tPA trials. We cannot exclude that these imbalances may influence our results. However, because no randomized controlled data are available, our analysis represents the highest available level of evidence for the use of MRI to select patients for treatment with IV-tPA in an expanded time window of up to 6 hours (level of evidence 2+).\textsuperscript{30}

Conclusion

In our study of IV-tPA therapy within an expanded time window of 6 hours in MRI-selected patients, outcome was better than in unselected patients from the pooled tPA stroke trials. Mortality and the frequency of severe bleeding complications were lower or comparable. In MRI-selected patients, outcome was not related to OTT time. In accordance to previous studies, treatment with IV-tPA within 6 hours in patients selected by MRI appears to be safe and more effective than IV thrombolysis in unselected patients. These findings support the potential role of MRI to identify stroke patients with tissue at risk of infarction that are likely to benefit from thrombolysis in an expanded time window. The future of acute stroke therapy may not be a “one size fits all” approach based on clock time but likely more of an individually tailored procedure based on imaging findings.

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