MRI-Based and CT-Based Thrombolytic Therapy in Acute Stroke Within and Beyond Established Time Windows
An Analysis of 1210 Patients

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Background and Purpose—The use of intravenous thrombolysis is restricted to a minority of patients by the rigid 3-hour time window. This window may be extended by using modern imaging-based selection algorithms. We assessed safety and efficacy of MRI-based thrombolysis within and beyond 3 hours compared with standard CT-based thrombolysis.

Methods—Five European stroke centers pooled the core data of their CT- and MRI-based prospective thrombolysis databases. Safety outcomes were predefined as symptomatic intracranial hemorrhage and mortality. Primary efficacy outcome was a favorable outcome (modified Rankin Scale 0 to 1). We performed univariate and multivariate analyses for all end points, including age, National Institutes of Health Stroke Scale, treatment group (CT <3 hours, MRI <3 hours and >3 hours), and onset to treatment time as variables.

Results—A total of 1210 patients were included (CT <3 hours: N=714; MRI <3 hours: N=316; MRI >3 hours: N=180). Median age, National Institutes of Health Stroke Scale, and onset to treatment time were 69, 67, and 68.5 years (P=0.66); 12, 13, and 14 points (P=0.019); and 130, 135, and 240 minutes (P<0.001). Symptomatic intracranial hemorrhage rates were 5.3%, 2.8%, and 4.4% (P=0.213); mortality was 13.7%, 11.7%, and 13.3% (P=0.68). Favorable outcome occurred in 35.4%, 37.0%, and 40% (P=0.51). Age and National Institutes of Health Stroke Scale were independent predictors for all safety and efficacy outcomes. The overall use of MRI significantly reduced symptomatic intracranial hemorrhage (OR: 0.520, 95% CI: 0.270 to 0.999, P=0.019). Within 3 hours, the use of MRI significantly predicted a favorable outcome (OR: 1.467; 95% CI: 1.017 to 2.117, P=0.040). Within 3 hours and for all secondary end points, there was a trend in favor of MRI-based selection over standard <3-hour CT-based treatment.

Conclusion—Despite significantly longer time windows and significantly higher baseline National Institutes of Health Stroke Scale scores, MRI-based thrombolysis is safer and potentially more efficacious than standard CT-based thrombolysis. (Stroke. 2007;38:2640-2645.)

Key Words: diffusion–perfusion mismatch ■ intravenous thrombolysis ■ MRI ■ stroke

Thrombolytic therapy with recombinant tissue plasminogen activator is currently approved for the treatment of acute ischemic stroke within 3 hours after symptom onset after CT-based exclusion of symptomatic intracerebral hemorrhage (sICH).1,2 Although thrombolytic therapy is at present the only approved treatment for this devastating disease, a substantial number of patients with acute stroke cannot be treated according to current guidelines.3 The diagnostic superiority of MRI for acute stroke has been firmly established.4–6 In the last years, an increasing number of reports and two small phase 2 studies (N=57 and N=37 patients) have suggested that a preselection of patients with multiparametric MRI protocols using diffusion-weighted (DWI) and perfusion imaging (PI) can identify patients with stroke who may benefit from intravenous thrombolysis within and beyond 3 hours after stroke symptom onset.7–13 Data from these studies suggest that there is an improved safety with regard to mortality and sICH as well as an increased treatment benefit of such selected patients, and the recently published DEFUSE study defined MRI profiles that predict favorable as well as unfavorable outcomes.13 Our objective was to investigate safety and efficacy of MRI-based thrombolytic therapy within and beyond the 3-hour time window compared with standard CT-based treatment within 3 hours.
Methods

By pooling the prospective intravenous thrombolysis databases of 5 European stroke centers (Heidelberg [HD], Hamburg [HH], Cologne [KO], Frankfurt [FAM], Barcelona [BA]), we performed a multicenter analysis in a total of 1210 patients treated with standard-dose recombinant tissue plasminogen activator (0.9 mg/kg body weight, 10% as bolus, rest as 1-hour infusion). All stroke centers started their databases in the late 1990s or early 2000s. Data sets were compared for a common and complete set of variables. All centers assessed patient age, gender, side of infarction, time from stroke symptom onset to treatment, baseline stroke severity according to the National Institutes of Health Stroke Scale (NIHSS),14 3-month outcome, and sICH defined like in the National Institute of Neurological Disorders and Stroke study.1 We defined 3 groups of patients: (1) patients receiving CT-based thrombolysis within 3 hours, (2) patients with MRI-based thrombolysis within 3 hours, and (3) patients treated MRI-based beyond 3 hours. All patients received standardized supportive treatment according to national and international guidelines15 and were not included in any stroke trial and had not received any drug or procedure under investigation. Smaller parts of the data sample were published before by 2 of the participating centers.11,12

Treatment was performed according to CT-based approval or established stroke MRI selection algorithms.7,13,17 The category was defined by the treatment interval, not the imaging modality, ie, if time to MRI <3 hours and onset to treatment time >3 hours, then the patient was categorized into MRI-based treatment beyond 3 hours. MRI patients within 3 hours and all patients beyond the 3-hour time window were treated based on a PI/DWI mismatch of approximately 20% by eyeballing the lesions. All centers used 1.5-Tesla MRI scanners. In between centers, the DWI sequences did not differ. PI methods varied slightly. Minor differences in sequence specifications for PI do not matter for clinical purposes. Two centers used black-and-white MTI (MMT) and TDP (BA) parameter maps without postprocessing or thresholding as shown on the monitor directly after image acquisition for decision-making. Three centers (HH, FAM, CO) applied 4-second thresholds to their TTP maps; 2 of these centers (FAM, HH) used an arterial input function and SVD (Ostergaard) method for generation of their maps.18 Within the 3-hour time window, patients were treated either by CT or MRI criteria. Three centers used MRI as the default imaging modality (BA, FAM, HH) and 2 centers (KO, HD) used CT as the default imaging modality within 3 hours. Within the 3-hour time window, centers used the alternate imaging modality instead either within institutional protocols, eg,5 or used the one modality available at the earliest time point. None of the centers used additional CT angiography or perfusion CT for patient evaluation. In the participating centers, ASPECTS score19 was not used to select or exclude patients from therapy; however, large and well-demarcated lesions exceeding one third of the middle cerebral artery territory were an exclusion criterion for thrombolysis in the institutional protocols of all centers. All statistical analyses were performed using the SPSS software package (SPSS 13.0; www.spss.com). Because all continuous data were not normally distributed (Kolmogorov-Smirnov test), nonparametric tests were applied and values are expressed as median and range. For all analyses, a 2-tailed value of P<0.05 was considered statistically significant and Bonferroni correction was used for post hoc testing (Mann-Whitney U test). We a priori predefined our safety, primary and secondary efficacy end points before the data sets were compiled. Safety end points were sICH and mortality, the primary efficacy outcome was favorable versus unfavorable (mRS 0 to 1 versus 2 to 6), and secondary efficacy outcomes were independent versus dependent or dead (mRS 0 to 2 versus 3 to 6) and responder analysis.20 Day 90 responder mRS score is dependent on baseline NIHSS; baseline NIHSS 0 to 7 had to obtain mRS 0, NIHSS 8 to 14 mRS 0 to 1, and NIHSS >14 mRS 0 to 2 to be rated as a responder. After univariate analysis, we performed forward stepwise logistic regression models to investigate influences of clinical and neuroradiological parameters on all 5 dichotomized end points.

Results

Patients, Onset to Treatment Time, and National Institutes of Health Stroke Scale

We analyzed 1210 patients (55.5% male, 52.6% left-sided infarct). Of these, 714 were treated CT-based (group 1), and 316 and 180 were treated MRI-based within (group 2) and beyond 3 hours (group 3), respectively. Patient age was not different between groups (P=0.664); time from symptom onset to treatment (P<0.001) and NIHSS (P=0.019) differed significantly between groups (Jonckheere-Terpstra test). In post hoc comparisons, the time window in group 3 naturally was longer than in groups 1 and 2 (both P<0.001), whereas treatment within 3 hours was not significantly delayed in MRI- versus CT-treated patients (135 versus 130 minutes, P=0.18). To more accurately assess whether the use of MRI <3 hours is associated with an inappropriate increase of onset to treatment time compared with CT, we categorized these patients into 3 additional groups (0 to 90 minutes, 155 patients; 91 to 120 minutes, 294 patients; and 121 to 180 minutes, 581 patients). Within these subsets (Figure), onset to treatment time between CT- and MRI-based patients did not differ (all P>0.075). For 0 to 90 minutes, it was a median of 85 versus 90 minutes (mean±SD 77.4±16.0 minutes versus 81.1±13.2 minutes). For 91 to 120 minutes, it was a median of 110 versus 115 minutes (mean±SD 110.6±8.8 minutes versus 112.7±8.3 minutes). For 121 to 180 minutes, it was a median of 150 versus 152 minutes (mean±SD 154.2±17.1 minutes versus 155.4±18.2 minutes).

Neither in univariate nor in multivariate analysis was onset to treatment time a predictor for any safety or efficacy outcome (all OR: 1.000 to 1.002, all P=0.5). Post hoc comparisons for NIHSS showed a trendwise higher stroke severity in group 2 than 1 (P=0.092) and a significantly higher NIHSS in group 3 than 1 (P=0.048). For patient characteristics, see Table 1.

Safety Outcomes

sICH occurred in 4.5% of all patients; mortality was 13.1%. Independent predictors for sICH were age (OR: 1.033, 95% CI: 1.006 to 1.060, P=0.016) and NIHSS (OR: 1.057, 95% CI: 1.010 to 1.106, P=0.016). Furthermore, the use of MRI was associated with a significantly reduced chance for sICH, albeit with a broad confidence interval (OR: 0.520, 95% CI: 0.270 to 0.999, P=0.05). For mortality, only age (OR: 1.072, 95% CI: 1.052 to 1.093, P<0.001) and NIHSS (OR: 1.115, 95% CI: 1.080 to 1.150, P<0.001) were independent predictors.

Efficacy Outcomes

A favorable outcome (primary end point, mRS 0 to 1) was seen in 36.5% of all patients. Independent outcome was achieved by 50.3% and response was seen in 33.5%. For the primary outcome besides age and NIHSS (OR: 0.973 and 0.862, both P<0.001), being treated based on MRI findings >3 hours compared with CT was an independent predictor for a favorable outcome (OR: 1.467, 95% CI: 1.017 to 2.117, P=0.040). Within 3 hours, there was only a trend for superiority of MRI over CT (OR: 1.136, 95% CI: 0.841 to 1.534). For the secondary outcomes (independent outcome,
responder analysis), only age and NIHSS were independent predictors (OR: 0.955 and 0.970 for age, both $P<0.001$; OR: 0.837 and 0.969 for NIHSS, $P<0.001$ and $P=0.005$). However, there were nonsignificant trends in favor of MRI- over CT-based selection for independent outcome (OR: 1.176, 95% CI: 0.905 to 1.529) and responder analysis (OR: 1.148, 95% CI: 0.879 to 1.501). For these trends, there was no difference between MRI-based treatment within or beyond 3 hours. For all multivariate models, the Hosmer Lemeshow test showed that the model adequately fits the data (all $P>0.1$). For univariate analyses of safety and efficacy outcomes, see Tables 2 and 3.

We performed a post hoc analysis of center effect on safety and efficacy outcomes: for all outcomes, overall and within the 3 treatment groups, there are no significant differences in both MRI arms and only small differences in the CT arm for responder analysis and hemorrhage rates, which are explained by differences in median NIHSS (up to 5 points) and age (up to 11 years) in these respective subgroups.

**Discussion**

Approved treatment strategies for acute stroke currently are limited to intravenous thrombolysis with recombinant tissue plasminogen activator within 3 hours after CT-based exclu-

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**Table 1. Baseline Parameters: Median and Range for Age, NIHSS, and Time From Symptom Onset to Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (CT &lt;3 hours)</th>
<th>Group 2 (MR &lt;3 hours)</th>
<th>Group 3 (MR &gt;3 hours)</th>
<th>$P$ Value (Jonckheere-Terpstra)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median/range)</td>
<td>69 (21–94)</td>
<td>67 (19–91)</td>
<td>68.5 (26–91)</td>
<td>0.664</td>
</tr>
<tr>
<td>NIHSS (median/range)</td>
<td>12 (1–37)</td>
<td>13 (0–28)</td>
<td>14 (2–42)</td>
<td>0.019</td>
</tr>
<tr>
<td>Time from symptom onset to treatment, minutes (median/range)</td>
<td>130 (10–180)</td>
<td>135 (40–180)</td>
<td>240 (181–1032)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Univariate analysis by Jonckheere-Terpstra square test, 2-sided $P$ values.*
sion of intracerebral hemorrhage\textsuperscript{21} or to aspirin within 48 hours, the latter with only a minimal effect.\textsuperscript{2} Although recently, devices for interventional revascularization have been approved, their clinical efficacy remains unproven.\textsuperscript{22} Meta-analyses of CT-based thrombolytic therapy studies suggest an effect of intravenous thrombolysis beyond the 3-hour time window; however, no single trial has shown this beyond doubt\textsuperscript{23} and further trials such as ECASS 3 and IST-3 are pending.\textsuperscript{24,25} Although standard thrombolysis is feasible, efficacious, and reasonably safe in acute ischemic stroke as has been shown in several large registries over the last decade and most recently in the SITS-MOST study, still only a small fraction of patients with stroke are treated. Consequently, almost all stroke experts have for years been calling for an extension of the narrow 3-hour time window,\textsuperscript{7} which, however, may be associated with a loss of safety and efficacy in unselected patients.\textsuperscript{23} Multiparametric MRI using DWI and PI has been proven to be superior to CT in the diagnosis of acute ischemic and hemorrhagic stroke, and the authors concluded that MRI should be the “preferred test for accurate diagnosis of patients with acute suspected stroke.”\textsuperscript{4,6} The first series evaluating the PI/DWI mismatch concept for thrombolysis in clinical application have been published in the late 1990s.\textsuperscript{26} In a simplified approach, the area of decreased diffusion represents the ischemic core of the infarct and the perfusion/diffusion mismatch is believed to be a marker for critically hypoperfused yet potentially salvageable brain tissue (presumptive ischemic penumbra).\textsuperscript{7,27} Recent prospective yet open and nonrandomized analyses with blinded end point assessment suggested that MRI-based treatment yields a comparable or higher safety with regard to symptomatic bleedings and mortality and seems to be at least as effective as standard CT-based thrombolysis.\textsuperscript{11,12} The concept of mismatch-based selection has been successfully tested for patients in phase 2 studies of desmoteplase.\textsuperscript{9,10} Finally, the selection paradigm, the so-called PI/DWI mismatch concept, has again been confirmed in the DEFUSE study as useful to identify patients, who may benefit and differentiate them from those who may be harmed by thrombolytic therapy beyond 3 hours.\textsuperscript{13} There were no safety concerns with increasing body weight-adjusted dosages of desmoteplase in the DIAS and DEDAS studies of MRI-based thrombolytic therapy beyond 3 hours, and there was also a clear efficacy signal resulting in the DIAS 2 trial. As reported recently at the European Stroke Conference 2007 in Glasgow, DIAS-2 was negative for the primary efficacy end point for unclear reasons. There was no safety issue regarding increased bleeding rates. A trend for increased mortality in the high dose arm was only due to non-neurological deaths. Post hoc analyses have not been presented yet; however, failure of DIAS-2 might have been caused by several things, such as introducing heterogeneity by allowing for perfusion CT-based inclusion, small numbers, lower clinical severity and maybe too low a dosage of active drug. In DEFUSE, the authors prospectively treated patients CT-based in the 3- to 6-hour time window with recombinant tissue plasminogen activator and performed additional stroke MRI before and after thrombolysis. In brief, they showed that patients with a PI/DWI “target” mismatch had significantly increased odds of achieving a favorable outcome, whereas patients without a mismatch or with large lesions at baseline, a so-called malignant profile, did not. In DEFUSE, the sICH rate was 6.5% in patients with a target mismatch; a favorable clinical response was seen in 46%. The overall rate of symptomatic bleeding in DEFUSE was 9.5%. This poorer safety profile may be explained by the fact that using a CT-based selection algorithm does not filter out those patients in whom thrombolysis would not be given based on MRI findings. Therefore, in fact, DEFUSE finally delivered the proof of concept for a MRI-based selection algorithm using the target mismatch. This algorithm has been widely used before in clinical routine and in studies such as ours or others.

### Table 2. Percentages of Safety and Efficacy Outcomes by Groups 1 to 3*

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (CT &lt;3 hours) (N=714)</th>
<th>Group 2 (MR &lt;3 hours) (N=322)</th>
<th>Group 3 (MR &gt;3 hours) (N=174)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sICH, %</td>
<td>5.3</td>
<td>2.8</td>
<td>4.4</td>
<td>0.213</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>13.7</td>
<td>11.7</td>
<td>13.3</td>
<td>0.675</td>
</tr>
<tr>
<td>mRS 0–1, %</td>
<td>35.4</td>
<td>37.0</td>
<td>40.0</td>
<td>0.512</td>
</tr>
<tr>
<td>mRS 0–2, %</td>
<td>49.7</td>
<td>53.2</td>
<td>47.8</td>
<td>0.451</td>
</tr>
<tr>
<td>Responder, %</td>
<td>32.2</td>
<td>35.4</td>
<td>35.0</td>
<td>0.536</td>
</tr>
</tbody>
</table>

*Univariate analysis by χ² test, 2-sided P values. For logistic regression analysis, see text.

### Table 3. Safety and Efficacy Outcomes CT Versus All MRI*

<table>
<thead>
<tr>
<th></th>
<th>All CT (N=714)</th>
<th>All MRI (N=496)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sICH, %</td>
<td>5.3</td>
<td>3.4</td>
<td>0.120</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>13.7</td>
<td>12.3</td>
<td>0.470</td>
</tr>
<tr>
<td>mRS 0–1, %</td>
<td>35.4</td>
<td>38.1</td>
<td>0.343</td>
</tr>
<tr>
<td>mRS 0–2, %</td>
<td>49.7</td>
<td>51.2</td>
<td>0.610</td>
</tr>
<tr>
<td>Responder, %</td>
<td>32.2</td>
<td>35.3</td>
<td>0.266</td>
</tr>
</tbody>
</table>

*Percentages of safety and efficacy outcomes by groups 1 versus 2 + 3. Univariate analysis by χ² test, 2-sided P values. For logistic regression analysis, see text.
study and the CASES and SITS registries with similar or better safety and similar or better efficacy outcome rates. In congruence with findings of others, MRI-based treatment within 3 hours is feasible and does not cause major delays. In our data set, the time differences were minimal and probably negligible even within subdivisions of the 3-hour time window. Door to needle times were not available for analysis, but the fact that more than 300 patients were treated no later by MRI-based than CT-based selection within the 3-hour time window suggests that there is no relevant delay. Furthermore, our median onset to treatment time of 240 minutes in 180 patients treated beyond 3 hours and up to 17 hours (group 3) compares favorably with the DEFUSE study (treatment window 3 to 6 hours, 74 patients, median onset to treatment time 328 minutes). Interestingly, there was no significant center effect in the MRI groups, which may be caused by the more standardized and harmonized selection algorithm than excluding intracerebral hemorrhage and large or old infarctions by noncontrast CT. Furthermore, this again suggests a superior diagnostic accuracy of stroke MRI, because findings appear to be easier to interpret compared with CT; however, we did not assess diagnostic parameters such as sensitivity and specificity.

In the extended time window, MRI-based treatment significantly increased the odds for our predefined primary end point—a favorable outcome—by 46.7% compared with CT-based treatment within 3 hours despite a substantially longer time window (nearly a 2-hour difference) and a significantly higher baseline stroke severity (2-point difference). Secondary efficacy parameters also showed a trend for improved outcomes when MRI-based selection algorithms are applied. Furthermore, the use of MRI instead of CT significantly reduced the odds of sICH by nearly half. This finding is in line with previous studies of our groups and of the DIAS and DEDAS studies. Again, age and initial stroke severity are established as the most important predictors for safety and efficacy outcomes.

Limitations of our study include the nonrandomized and nonplacebo-controlled design using a compiled data set of 5 distinct centers. This introduces a bias because of heterogeneity of the data and the centers. Especially in some of the centers, patients may have been more likely to be treated based on CT within 3 hours than MRI, and in other centers vice versa. The post hoc center effect analysis clearly illustrates a lack of harmonization with regard to standard CT-based treatment, especially regarding age and NIHSS limits. However, the center effect analysis also illustrates that MRI selection is rather harmonized due to the mismatch-based selection process, which essentially followed in all centers the now published “DEFUSE criteria.” A selection bias cannot be excluded because of the nonrandomized design of our study. This, however, seems unlikely because patients treated based on MRI findings (1) had worse strokes and (2) were treated significantly later. Also, we cannot exclude that some patients may have been shifted from CT to MRI because of their closing in to the end of the 3-hour time window. Furthermore, due to the lack of a screening log, we cannot provide information about patients in whom treatment was withheld due to MRI findings. In all likelihood, these patients match the population, which did not profit in the DEFUSE study, i.e., PI/DWI matching patients and those with large DWI and PI lesions—the so-called malignant profile. Last but not least, varying PI algorithms may cause heterogeneity as to what is considered to be a mismatch.

In conclusion, we present a prospectively collected and to date the largest database of MRI-versus CT-based thrombolytic treatment in patients with acute stroke. Our study complements the findings of more rigorously designed, although far smaller, prospective studies. Our blinded assessment of safety and efficacy outcomes in a real life setting of 5 stroke centers and the predefined end points add to the credibility of our results, which are in line with the findings of recent proof of concept studies, smaller prospective series, and phase 2 studies. Overall, MRI-based thrombolysis appears to be safer and more effective than standard CT-based thrombolytic therapy for acute ischemic stroke. It does not cause a significant time loss, and the type of patients selected by this algorithm seems to be fairly homogeneous among different centers. The positive impact of MRI-based patient selection is accentuated beyond the 3-hour time window. Therefore, within the 3-hour time window, the choice of imaging modality may be at the discretion of the treating physician and depend on institutional protocols, although evidence from the recent literature shows a diagnostic superiority of MRI over CT. Beyond the 3-hour time window, however, a substantial number of patients can be treated with thrombolytic therapy based on a penumbral pattern as seen on stroke MRI. This of course does not imply that within 3 hours, CT-based thrombolysis should be deferred until one can treat MRI-based beyond 3 hours. Nevertheless, the safety and efficacy profile of MRI-based thrombolysis beyond 3 hours compares favorably to standard CT-based treatment.

Disclosures
P.D.S., G.T., T.N.H., and J.S. received speaker’s honoraria and travel stipends by the manufacturer of rt-PA (Boehringer-Ingelheim Pharma AG, Ingelheim, Germany).

References


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