The Desmoteplase in Acute Ischemic Stroke Trial (DIAS)

A Phase II MRI-Based 9-Hour Window Acute Stroke Thrombolysis Trial With Intravenous Desmoteplase

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Background and Purpose—Most acute ischemic stroke patients arrive after the 3-hour time window for recombinant tissue plasminogen activator (rtPA) administration. The Desmoteplase In Acute Ischemic Stroke trial (DIAS) was a dose-finding randomized trial designed to evaluate the safety and efficacy of intravenous desmoteplase, a highly fibrin-specific and nonneurotoxic thrombolytic agent, administered within 3 to 9 hours of ischemic stroke onset in patients with perfusion/diffusion mismatch on MRI.

Methods—DIAS was a placebo-controlled, double-blind, randomized, dose-finding phase II trial. Patients with National Institute of Health Stroke Scale (NIHSS) scores of 4 to 20 and MRI evidence of perfusion/diffusion mismatch were eligible. Of 104 patients, the first 47 (referred to as Part 1) were randomized to fixed doses of desmoteplase (25 mg, 37.5 mg, or 50 mg) or placebo. Because of an excessive rate of symptomatic intracranial hemorrhage (sICH), lower weight-adjusted doses escalating through 62.5 μg/kg, 90 μg/kg, and 125 μg/kg were subsequently investigated in 57 patients (referred to as Part 2). The safety endpoint was the rate of sICH. Efficacy endpoints were the rate of reperfusion on MRI after 4 to 8 hours and clinical outcome as assessed by NIHSS, modified Rankin scale, and Barthel Index at 90 days.

Results—Part 1 was terminated prematurely because of high rates of sICH with desmoteplase (26.7%). In Part 2, the sICH rate was 2.2%. No sICH occurred with placebo in either part. Reperfusion rates up to 71.4% (P = 0.0012) were observed with desmoteplase (125 μg/kg) compared with 19.2% with placebo. Favorable 90-day clinical outcome was found in 22.2% of placebo-treated patients and between 13.3% (62.5 μg/kg; P = 0.757) and 60.0% (125 μg/kg; P = 0.0090) of desmoteplase-treated patients. Early reperfusion correlated favorably with clinical outcome (P = 0.0028). Favorable outcome occurred in 52.5% of patients experiencing reperfusion versus 24.6% of patients without reperfusion.

Conclusions—Intravenous desmoteplase administered 3 to 9 hours after acute ischemic stroke in patients selected with perfusion/diffusion mismatch is associated with a higher rate of reperfusion and better clinical outcome compared with placebo. The sICH rate with desmoteplase was low, using doses up to 125 μg/kg. (Stroke. 2005;36:66-73.)

Key Words: desmoteplase ■ magnetic resonance imaging ■ stroke ■ thrombolytic therapy

Outcome after acute ischemic stroke (AIS) is improved by IV thrombolysis with recombinant tissue plasminogen activator (rtPA), which is the only approved drug for AIS. However, the use of IV rtPA is currently limited by the need to administer it within 3 hours of symptom onset.1 Clinical trials investigating IV thrombolytics in AIS in later time windows (Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS], European Cooperative Acute Stroke Study [ECASS], and ECASS II) have failed to show a significant benefit beyond 3 hours. A pooled analysis of these trials suggests a benefit up to 270 minutes, but not up to 6 hours.2-5 A wider time-to-treatment window may be achievable using a thrombolytic drug with a better safety and efficacy profile in patients selected by modern MRI technology, which, for clinical purposes, may identify ischemic penumbra.
Because of its high fibrin specificity, nonactivation by β-amyloid, and long terminal half-life, the plasminogen activator recombinant Desmotsalivary Plasminogen Activator α-1 (rDSPA α-1 or desmoteplase) is an attractive thrombolytic agent. Another possible advantage is the absence of neurotoxicity compared with rtPA.6–7 A common MRI profile in patients with AIS is an area of perfusion deficit on perfusion MRI (pMRI) that is larger than the lesion on diffusion-weighted imaging (DWI) that may partly reflect irreversibly damaged brain tissue. This perfusion/diffusion mismatch is believed to be a marker of salvageable brain tissue (presumptive ischemic penumbra), provided that perfusion can be restored early enough.8–10 The objective of the Desmoteplase In Acute Ischemic Stroke trial (DIAS) was to explore the safety and efficacy of various doses of IV desmoteplase in patients with AIS and perfusion/diffusion mismatch on MRI up to 9 hours from stroke onset to establish the optimal dose for further study.

Patients and Methods

Patients, Dosages, and Sample Size Calculation

Between January 2001 and October 2003, 44 centers in 12 countries participated in this double-blind, placebo-controlled, randomized, dose-finding, phase II trial of desmoteplase for treatment of AIS. The protocol and all amendments received institutional review board approval at each center and written informed consent was obtained from all patients or their legal representative.

The original trial design planned to investigate 3 fixed doses of 25 mg, 37.5 mg, and 50 mg desmoteplase versus placebo in 4 parallel groups of 30 patients each (hereafter called Part 1). These doses were chosen based on safety findings from a preliminary trial in patients with myocardial infarction, because they were not associated with fibrinogen depletion. Trial drug was administered as an IV bolus over 1 to 2 minutes. Stratification according to age (≤75 versus >75) and baseline National Institute of Health Stroke Scale (NIHSS; ≤14 versus >14) was performed. Treatment allocation was performed through an interactive voice response system collecting patient’s date of birth, weight, and NIHSS score. Patients were randomized to a dose of desmoteplase or placebo. Patients ≤66 kg were administered 80% of the dose, those ≥66 kg received 100%. An independent Data Monitoring Committee (DMC) monitored hemorrhages and other adverse events using prospectively defined stopping rules.

After enrollment of the 30th patient, the occurrence of 3 symptomatic intracranial hemorrhages (sICHs) in the 37.5 mg group and 1 in the 50 mg group resulted in discontinuation of these doses by the DMC. The trial continued with 25 mg and placebo. After the 47th patient was recruited, excess sICH rates in the 25 mg group prompted a halt by the DMC, an interim analysis, and subsequent protocol amendment.

The trial recommenced (Part 2) using a placebo-controlled bodyweight-adjusted dose-escalation design starting at a dose of 62.5 μg/kg, followed by 90 μg/kg and 125 μg/kg. Each dose tier included 15 desmoteplase patients and 4 placebo patients. No stratification was implemented.

Inclusion and Exclusion Criteria

Eligible patients were aged 18 to 85 years, scored 8 to 20 on NIHSS, showed at least 20% perfusion/diffusion mismatch (as evaluated by visual inspection) involving hemispheric gray matter, and could be treated within 3 to 6 hours after stroke onset. Exclusion criteria were similar to those adopted by other thrombolytic trials. Several adjustments in eligibility criteria were made during the course of the trial.

1. After 5 patients were included in Part 1, a 30-minute MRI-to-treatment time requirement was applied to minimize the possibility of spontaneous MRI changes between scan acquisition and start of treatment. In addition, the upper limit for the DWI lesion at baseline was reduced from two thirds to one third of the middle cerebral artery (MCA) territory to limit the risk of bleeding, and patients taking any platelet function inhibitor were excluded if administering the trial medication might add an additional risk of hemorrhage in the judgment of the investigator.

2. To enhance recruitment, after the enrollment of 9 patients, the baseline NIHSS range was extended from 8 to 20 to 4 to 20 and the onset-to-treatment time window was widened from 3 to 6 to 3 to 9 hours. The selection of patients based on perfusion/diffusion mismatch and DWI lesion size was considered a theoretical safeguard allowing the expansion of the time window.

3. After the interim analysis of Part 1, the upper limit of baseline blood sugar was reduced from 22 to 11 mmol/L because an analysis of risk factors for ICH revealed an association with blood glucose level >10 mmol/L (Table 1).

MRI Examinations

MRI was performed at screening, 4 to 8 hours posttreatment, and 30 days follow-up. The screening and 4 to 8 hour MRI consisted of a scout, single shot echo-planar DWI, 3D time-of-flight magnetic resonance angiography (MRA) of the intracranial circulation, fluid-attenuated inversion recovery (FLAIR), and bolus-tracking susceptibility (T2*) weighted pMRI using intravenous gadolinium 0.1 mmol/kg at 5c/s. At 30 days, the MRI protocol was composed of scout, DWI and FLAIR.

All MRI scanners used were 1.5 T equipped with manufacturer head coils and echo-planar capability. Sequence parameters were standardized across matched scanner types and trial centers. Images were sent to a Core Imaging Laboratory (Perceptive) for processing and analysis. Although different analytic methods for pMRI (eg, mean transit time [MTT] and time-to-peak) were allowed at the centers, MTT maps were created based on the normalized first moment method at the Core Imaging Laboratory. Image analysis was performed blinded to dose assignment, clinical information, and trial center. In addition, the reader was blinded to the order of the baseline and 4- to 8-hour scans. Image analysis included volume of abnormality on DWI and MTT at baseline and 4 to 8 hours, volume of the chronic lesion on FLAIR, and presence of ICH. The degree of arterial stenosis or occlusion was also assessed, based on an adaptation of the Thrombolysis In Myocardial Infarction grading scheme: 0=complete occlusion, 1=severe stenosis, 2=mild to moderate stenosis, and 3=normal arterial caliber. The full details of MRI acquisition, analytic methods, and results will be the subject of a separate communication.

Endpoints

The primary safety endpoint was the rate of sICH defined as any ICH associated with a worsening of 4 points or more on the NIHSS and confirmed by computerized tomography within 72 hours of treatment. Other safety outcomes included major systemic bleeding, anaphylaxis, and mortality. Other adverse events and serious adverse events were also monitored.

The coprimary efficacy endpoints were perfusion and clinical outcome. Reperfusion was assessed 4 to 8 hours posttreatment and defined as either ≥30% reduction of MTT volume of abnormality or ≥2 points improvement on the adapted Thrombolysis In Myocardial Infarction grading scheme using MRA. The primary clinical endpoint was based on the combined analysis of the NIHSS, modified Rankin scale (mRS), and Barthel Index (BI) defined as ≥8 points improvement or scoring 0 to 1 on the NIHSS, a score of 0 to 2 on mRS, and a BI score of 75 to 100 at 90 days. The clinical status of the patient was also assessed at 4 to 8 hours, 7 days, and 30 days using the same scales. Other efficacy outcome measures included the change in infarct lesion volume on DWI from baseline to 30 days.

The DMC was immediately informed of each newly randomized patient, any hemorrhages occurring after treatment, and about the...
72-hour outcome of each patient. The DMC was unblinded and not involved in other trial tasks.

**Statistical Analysis**

Efficacy and safety analyses were performed for the intention-to-treat sample. Deceased patients were given the worst possible score for all outcomes. Other missing data were replaced by the last observation carried forward. Exploratory analyses included comparisons among the desmoteplase doses and between desmoteplase and placebo regarding all safety and efficacy parameters. Comparison of treatment groups was based on the odds ratio method. All group comparisons with 1-sided probability values
TABLE 2. Characteristics of Patients

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Placebo (n=16)</th>
<th>Desmoteplase (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1</td>
<td>25 mg*</td>
<td>37.5/50 mg*</td>
</tr>
<tr>
<td>Female, %</td>
<td>43.8 (12.5)</td>
<td>35.3 (17.6)</td>
</tr>
<tr>
<td>Age, y</td>
<td>67.5 (11)</td>
<td>65 (17)</td>
</tr>
<tr>
<td>NIHSS</td>
<td>12.5 (11)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Time from onset, min</td>
<td>320 (11)</td>
<td>330 (11)</td>
</tr>
<tr>
<td>DWI lesion volume, ml</td>
<td>14.99 (11)</td>
<td>14.49 (11)</td>
</tr>
<tr>
<td>Glucose level, mmol/L</td>
<td>6.53 (11)</td>
<td>6.83 (11)</td>
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</table>

<table>
<thead>
<tr>
<th>Total</th>
<th>Placebo (n=27)</th>
<th>Desmoteplase (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>48.1 (10)</td>
<td>45.3 (15)</td>
</tr>
<tr>
<td>Age, y</td>
<td>68 (15)</td>
<td>68 (15)</td>
</tr>
<tr>
<td>NIHSS</td>
<td>12 (15)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Time from onset, min</td>
<td>325 (15)</td>
<td>324 (15)</td>
</tr>
<tr>
<td>DWI lesion volume, ml</td>
<td>20.40 (15)</td>
<td>17.76 (15)</td>
</tr>
<tr>
<td>Glucose level, mmol/L</td>
<td>6.60 (15)</td>
<td>6.77 (15)</td>
</tr>
</tbody>
</table>

All values are median values except for Female. *Desmoteplase dose.

Concomitant Medication
In the first 24 hours after administration of trial medication, anticoagulants and antplatelet agents were not allowed for safety reasons. Thereafter, these agents could be used at the discretion of the investigator. The use of other thrombolytics was prohibited in the first 72 hours.

Investigator and Center Qualification
Only certified trial staff were allowed to perform NIHSS assessment on patients. Centers also had to qualify for the MRI procedures. Both the MRI Committee and the Core Imaging Laboratory assisted in designing the imaging protocol, recruiting centers with appropriate MRI equipment, handling imaging problems arising from the centers, and monitoring compliance with MRI procedures.

Results
A total of 104 patients were randomized into DIAS: 47 in Part 1 and 57 in Part 2. Two patients, randomized to receive placebo, received no trial medication because of the need for arterial puncture in 1 patient and a different interpretation of MRI findings after randomization for the other. Both patients were excluded from all analyses. The desmoteplase and placebo groups were balanced with regard to patient’s characteristics, except for a longer time from onset in the 90 μg/kg dose group and larger DWI lesion volumes in both the 90-μg/kg and 125-μg/kg dose groups (Table 2). Sixteen patients terminated the study prematurely because of death (n=10), consent-withdrawal (n=5), and loss to follow-up (n=1).

Part 1: Safety
Primary Safety Endpoint
sICHs were observed in 8 of 30 desmoteplase-treated patients (26.7%), of which 4 of 17 were in the 25-mg group (23.5%) and 4 of 13 in the 37.5/50-mg group (30.8%; Table 3). All sICHs occurred within the first 24 hours after treatment except one, which occurred at 25 hours. Protocol violations occurred in 2 patients with sICH: one received heparin within 24 hours and the other had a high baseline blood glucose level. No sICH occurred in placebo-treated patients. The high sICH rates resulted first in the discontinuation of the 50 mg and 37.5 mg doses and finally in trial suspension.

The desmoteplase dosages the patients received in Part 1 ranged from 227 μg/kg to 714 μg/kg when calculated on a weight basis. The lowest dose associated with sICH was 294 μg/kg.

Other Safety Endpoints
Mortality within 90 days was higher with active treatment. Seven deaths occurred, all among desmoteplase-treated patients. Deaths were secondary to sICH (n=4) or cardiopulmonary causes (n=3). Asymptomatic ICH occurred in 7

TABLE 3. Intracranial Hemorrhage

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Placebo (n=16)</th>
<th>Placebo (n=11)</th>
<th>Placebo (n=27)</th>
<th>Desmoteplase (n=75)</th>
<th>Total (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1</td>
<td>25 mg*</td>
<td>37.5/50 mg*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic ICH</td>
<td>No. (%) 2 (12.5)</td>
<td>3 (17.6)</td>
<td>2 (15.4)</td>
<td>2 (15.4)</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>95% CI [1.6; 38.3]</td>
<td>[3.8; 43.4]</td>
<td>[1.9; 45.4]</td>
<td>[6.0; 61.0]</td>
<td>[11.8; 61.6]</td>
<td>[16.3; 67.7]</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>No. (%) 0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>95% CI [0.0; 20.6]</td>
<td>[0.0; 21.6]</td>
<td>[0.0; 21.6]</td>
<td>[0.0; 21.6]</td>
<td>[0.0; 12.8]</td>
<td>[4.1; 16.1]</td>
</tr>
</tbody>
</table>

*Desmoteplase dose.
TABLE 5. Favorable Clinical Outcome at 90 Days*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Part 1</th>
<th>Part 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=16)</td>
<td>25 mg†</td>
<td>37.5/50 mg†</td>
<td>40</td>
</tr>
<tr>
<td>Placebo (n=10)</td>
<td>62.5 µg/kg†</td>
<td>90 µg/kg†</td>
<td>10</td>
</tr>
<tr>
<td>Placebo (n=26)</td>
<td>Desmoteplase (n=71)</td>
<td>Total (n=97)</td>
<td></td>
</tr>
</tbody>
</table>

No. (%) 4 (25.0) 2 (18.8) 7 (41.2) 2 (18.2) 2 (13.3) 7 (46.7) 9 (60.0) 6 (22.2) 35 (49.3) 40 (41.2)
95% CI [4.0; 45.6] [29.9; 80.2] [19.2; 74.9] [2.5; 55.6] [5.0; 53.8] [21.3; 73.4] [41.9; 91.6] [6.6; 39.4] [37.2; 61.4] [31.3; 51.7]
P values‡ 0.0086 0.0431 0.3897 0.0012 0.0054

All patients with assessable images.
†Desmoteplase dose; ‡vs placebo total.

Part 1: Efficacy

Reperfusion

The 4 to 8 hours posttreatment magnetic resonance (MR)-images of 1 desmoteplase-treated patient were missing. Early reperfusion at 4 to 8 hours after treatment was observed in 9 of 16 patients receiving 25 mg desmoteplase (56.3%), 7 of 13 receiving 37.5/50 mg desmoteplase (46.2%), and 3 of 16 placebo-treated patients (18.8%; Table 4).

Primary Clinical Endpoint

A favorable clinical outcome at 90 days was achieved in 7 of 17 desmoteplase-treated patients in the 25-mg group (41.2%), 4 of 13 in the 37.5/50-mg group (30.8%), and in 4 of 16 placebo-treated patients (25.0%; Table 5).

Part 2: Safety

Primary Safety Endpoint

No placebo-treated patients and 1 of 45 desmoteplase-treated patients (2.2%) had sICH; this patient received 90 µg/kg desmoteplase (Table 3).

Other Safety Endpoints

Three patients, 1 placebo-treated (9.1%) and 2 desmoteplase-treated (4.4%), died because of cardiac causes. Asymptomatic ICHs occurred in 17 patients (30.4%); 3 of 11 placebo-treated patients (27.3%) and 14 of 45 desmoteplase-treated patients (31.1%; Table 3). One major gastrointestinal hemorrhage occurred in the 62.5-µg/kg group on day 79.

Part 2: Efficacy

Reperfusion

MR-images of 3 desmoteplase-treated patients and 1 placebo-treated patient were either missing or not assessable. Early reperfusion at 4 to 8 hours after treatment was observed in 3 of 13 desmoteplase-treated patients in the 62.5-µg/kg group (23.1%), 7 of 15 in the 90-µg/kg group (46.7%), 10 of 14 in the 125-µg/kg group (71.4%), and in 2 of 10 placebo-treated patients (20%; Table 4 and Figure 1).

Primary Clinical Endpoint

There was a dose-dependent rate of favorable outcome at 90 days, with 13.3%, 46.7%, and 60% of patients in the 62.5-µg/kg, 90-µg/kg, and 125-µg/kg desmoteplase groups, respectively, showing a favorable clinical outcome compared with 18.2% in the placebo group (Table 5 and Figure 1).

Pooling placebo-treated patients from both Part 1 and Part 2 showed a reperfusion rate of 19.2% and a favorable clinical response in 22.2%. Compared with pooled placebo, the 125-µg/kg desmoteplase dose achieved significantly better results (reperfusion P=0.0012; favorable clinical outcome P=0.0090).

Other Analyses

In the 97 patients with assessable MR-images, a favorable clinical outcome at 90 days was achieved in 21 of 40 patients with reperfusion (52.5%) and 14 of 57 without reperfusion (24.6%). There was a significant correlation between reperfusion and favorable clinical outcome (P=0.0028).
In preclinical studies, desmoteplase demonstrated high fibrin specificity and selectivity, nonactivation by β-amyloid, a long half-life, and absence of neurotoxicity. These are potential advantages over other thrombolytic agents including rtPA. Desmoteplase has also been tested in a phase II trial in patients with myocardial infarction, where doses of 500 μg/kg and 750 μg/kg confirmed thrombolytic activity in humans without causing fibrinogen depletion. DIAS therefore began with a dose-ranging design investigating fixed doses between 25 mg (median=313 μg/kg) and 50 mg (median=546 μg/kg). However, these doses were associated with excessive sICH. Reducing the size of the qualifying DWI abnormality from a maximum of two thirds to one third of the MCA territory after 5 patients were treated did not produce any demonstrable decrease in the rate of sICH. Despite the high rate of sICH in Part 1, efficacy analyses suggested favorable trends in reperfusion rates and clinical outcome, and subsequent calculations based on the pharmacokinetics of desmoteplase indicated that doses lower than those tested might be safer and effective. The revised design Part 2 tested lower weight-adjusted doses of desmoteplase and confirmed that the high initial doses were the likely cause of the excessive rates of sICH in Part 1. Part 2 showed a favorable safety profile for the doses tested, with only 1 sICH among 45 desmoteplase-treated patients.

The MRI reperfusion rates of 46.7% and 71.4% at 4 to 8 hours after treatment with 90 μg/kg and 125 μg/kg of desmoteplase suggest a dose-dependent effect of desmoteplase and are supported by 90-day clinical response rates of 46.7% and 60%, respectively. Patients treated with 125 μg/kg of desmoteplase had better reperfusion and clinical response rates than the combined high-dose treatment groups (25 to 50 mg) from Part 1, which may reflect improved safety at this dose. The 62.5-μg/kg dose did not cause significant reperfusion.

The presence of larger baseline DWI lesions clustered in the 90-μg/kg and 125-μg/kg dose groups may have disadvantaged the desmoteplase groups; other baseline factors were reasonably balanced. The dose escalation design used in Part 2 generated a small risk that the central interpretation of MRI perfusion data could be influenced by knowledge of the likely dose group, although treatment allocation remained blinded.

A longer stroke onset to treatment interval was not associated with a reduction of treatment effect, which suggests that beyond 3 hours from onset of stroke the presence of perfusion/diffusion mismatch as a marker of tissue at risk may be a more important predictor of therapeutic response than duration of symptoms.

There was also a positive correlation (P=0.0028) between reperfusion and clinical outcome. These findings are in line with a recent report of patients receiving IV rtPA, which found that a decrease in the volume of pretreatment MTT defect of ≥30% 2 to 3 hours after treatment was a highly significant predictor of clinical recovery (mRS 0 or 1).11

Among patients with no reperfusion on MRI, there was a 50% favorable outcome rate in both the 90-μg/kg and 125-μg/kg dose groups compared with 10% in the 62.5-μg/kg group. The rate in the placebo group was 9.5%. A
possible explanation could be that the long half-life of desmoteplase may have facilitated reperfusion after the 4 to 8 hour follow-up MRI scan in the 90-μg/kg and 125-μg/kg dose groups, whereas the low rate in the 62.5-μg/kg group further indicates the noneffectiveness of this dose.

In using a thrombolytic drug safely, one of the most important factors is the selection of patients with a low inherent risk of spontaneous hemorrhagic transformation. DIAS has confirmed that stroke severity and increasing age are important predictors of sICH but did not establish severity or age cutoff criteria beyond which treatment was unsafe.12–13 Mortality after desmoteplase was low and comparable to placebo in Part 2. In contrast to the pooled analysis of the ATLANTIS, ECASS and NINDS trials, which showed a constant risk of ICH over the first 5 hours after stroke onset with increasing risk in the 6th hour, DIAS found no time dependency of sICH risk comparing patients treated < or >5 hours from stroke onset.5

In conclusion, DIAS suggests that IV thrombolysis with desmoteplase 3 to 9 hours after stroke onset is safe in patients selected according to perfusion/diffusion mismatch on MRI and that dose dependent reperfusion on MRI is correlated with clinical outcome. Patients treated with desmoteplase between 6 and 9 hours of stroke onset had a clinical outcome that was as good as those treated within 3 to 6 hours. This finding supports the concept of shifting from a general ticking-clock to an individualized tissue-clock in ischemic stroke. However, all these findings need to be confirmed and studied in larger trials.

Appendix

The following centers recruited patients to DIAS (center, principal investigator, and number of patients): Heidelberg, Germany: Hacke and Ringleb (17); Leipzig, Germany: Schneider (11); Lausanne, Switzerland: Bogousslavsky (10); Girona, Spain: Davalos (9); Hamburg, Germany: Weiller (9); Linz, Austria: Aichner (7); Bordeaux, France: Rouanet (6); Paris, France: Chabriat (6); Singapore: Chang (5); Graz, Austria: Fazekas (3); Ulm, Germany: Huber (3); Paris, France: Touzé (2); St Gallen, Switzerland: Weder (2); Munich, Germany: Sander (2); Melbourne, Australia: Davis (1); New Lambton Heights, Australia: Levi (1); Brussels, Belgium: Bleic (1); Helsinki, Finland: Kaste (1); Lyon, France: Trouillas (1); Paris, France: Samson (1); Bochum, Germany: Meves (1); Frankfurt, Germany: Steinmetz (1); Freiburg, Germany: Hetzel (1); Bergen, Norway: Thomassen (1); Badalona, Spain: Vila (1); and Aberdeen, Great Britain: MacLeod (1).

Steering Committee: Werner Hacke (Chair), Anthony Furlan, Markku Kaste, Michael Eliasziw, Michael Fischer, Mariola Soehngen, and Yasir Al-Rawi. Greg Albers participated in Part 1 of DIAS.
MRI Committee: Steven Warach (Chair), Julien Bogousslavsky, and Howard Rowley. Marc Fisher participated in Part 1 of DIAS.

DMC: Kennedy Lees (Chair), Lawrence Wechsler, Rudiger von Kummer, and Walter Lehmaccher. Claus-Steffen Steuerzebecher and Klaus Poeck participated in Part 1 of DIAS.

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