Magnetic Resonance Imaging Profiles Predict Clinical Response to Early Reperfusion: The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) Study

Gregory W. Albers, MD,[1] Vincent N. Thijs, MD, PhD,[3] Lawrence Wechsler, MD,[4] Stephanie Kemp, BS,[1] Gottfried Schlaug, MD, PhD,[5] Elaine Skalabrin, MD,[6] Roland Bammer, PhD,[2] Wataru Kakuda, MD,[1] Maarten G. Lansberg, MD, PhD,[1] Ashfaq Shuaib, MD,[7] William Coplin, MD,[7] Scott Hamilton, PhD,[1] Michael Moseley, PhD,[2] and Michael P. Marks, MD,[2] for the DEFUSE Investigators

Objective: To determine whether prespecified baseline magnetic resonance imaging (MRI) profiles can identify stroke patients who have a robust clinical response after early reperfusion when treated 3 to 6 hours after symptom onset.
Methods: We conducted a prospective, multicenter study of 74 consecutive stroke patients admitted to academic stroke centers in North America and Europe. An MRI scan was obtained immediately before and 3 to 6 hours after treatment with intravenous tissue plasminogen activator 3 to 6 hours after symptom onset. Baseline MRI profiles were used to categorize patients into subgroups, and clinical responses were compared based on whether early reperfusion was achieved.
Results: Early reperfusion was associated with significantly increased odds of achieving a favorable clinical response in patients with a perfusion/diffusion mismatch (odds ratio, 5.4; $p = 0.039$) and an even more favorable response in patients with the Target Mismatch profile (odds ratio, 8.7; $p = 0.011$). Patients with the No Mismatch profile did not appear to benefit from early reperfusion. Early reperfusion was associated with fatal intracranial hemorrhage in patients with the Malignant profile.
Interpretation: For stroke patients treated 3 to 6 hours after onset, baseline MRI findings can identify subgroups that are likely to benefit from reperfusion therapies and can potentially identify subgroups that are unlikely to benefit or may be harmed.

Ann Neurol 2006;60:508–517

Early reperfusion of ischemic brain tissue in acute stroke patients can salvage hypoperfused tissue and improve neurological outcome. Currently, the only approved pharmacological therapy for stroke treatment is a thrombolytic agent, tissue plasminogen activator (tPA), administered intravenously within 3 hours of symptom onset.[1,2] If the treatment window for effective reperfusion therapy can be expanded, considerably more stroke patients would be eligible for therapy.[3] Unfortunately, controlled trials of tPA administered beyond 3 hours have not demonstrated significant benefits.[4–7] This failure may have resulted from inclusion of patients who were unlikely to benefit from reperfusion therapy because they had minimal salvageable ischemic brain tissue or were at high risk for reperfusion-related complications such as cerebral edema or symptomatic intracranial hemorrhage (SICH).

Recent observations suggest that new magnetic resonance imaging (MRI) techniques have the potential to identify patients who are optimal candidates for reperfusion therapies in extended time windows.[8–16] A perfusion/diffusion mismatch has been proposed as a surrogate for the ischemic penumbra, and patients with a mismatch are hypothesized to be more likely to benefit from early reperfusion than patients with other MRI

From the [1]Department of Neurology and Neurological Sciences and the Stanford Stroke Center, Stanford University Medical Center, Stanford, CA; [2]Department of Radiology and the Stanford Stroke Center, Stanford University Medical Center, Stanford CA; [3]Department of Neurology, University Hospitals Leuven, Leuven, Belgium; [4]UPMC Stroke Institute and Department of Neurology, University of Pittsburgh, PA; [5]Division of Cerebrovascular Disorders, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston MA; [6]Department of Neurology, University of Utah, Salt Lake City, UT; and [7]Division of Neurology, Department of Medicine, University of Alberta, Edmonton, AB, Canada (AS).

Received Jul 15, 2006, and in revised form Aug 22. Accepted for publication Aug 22, 2006.

Published online Oct 25, 2006, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.20976

Address correspondence to Dr Albers, Department of Neurology and Neurological Sciences, Stanford University Medical Center, 701 Welch Road, Suite 325, Palo Alto, CA 94304.
E-mail: albers@stanford.edu

patterns.[9,11–13,15,16] However, this assumption has been questioned because a differential clinical response to early reperfusion (greater benefits in mismatch compared with nonmismatch patients) has not yet been demonstrated.[17–19]

Therefore, to help clarify whether clinical trials of reperfusion therapies that select patients with specific baseline MRI profiles are likely to be more successful than conventional stroke trials, we tested the hypothesis that patients with predefined MRI profiles would demonstrate a differential clinical response after successful early reperfusion. To achieve this goal, we administered intravenous tPA to consecutive patients regardless of their baseline MRI profile. We anticipated that about half of the tPA-treated patients would achieve early reperfusion and half would not. Assuming that early reperfusion would occur at approximately the same rate in patients with different MRI profiles, this design allowed us to assess associations between early reperfusion and clinical response with adequate power, using a relatively small sample of patients. This design also provided the opportunity to refine the definitions of specific MRI profiles to enhance their predictive potential. The primary hypothesis of the *D*iffusion and Perfusion Imaging *E*valuation *F*or *U*nderstanding *S*troke *E*volution (DEFUSE) study was that patients with a diffusion/perfusion mismatch would have a more favorable clinical response after early reperfusion compared with nonmismatch patients.

Patients and Methods

Patients were enrolled at university hospitals in the United States, Canada, and Belgium (see Appendix). The local institutional review board at each site approved the study and consent was obtained from each patient or an appropriate family member. Patients were eligible to participate if they were 18 years or older, had a clinical diagnosis of ischemic stroke with a National Institutes of Health Stroke Scale (NIHSS) score greater than 5, and could be treated with tPA within 3 to 6 hours after symptoms onset. Patients were excluded if they were comatose or severely obtunded, had rapidly improving symptoms, a history of stroke within the last 6 weeks, premorbid modified Rankin Scale (mRS) score of 3 or higher, seizure at symptom onset, previous intracranial hemorrhage, or evidence of acute hemorrhage or clearly identifiable hypodensity involving more than one third of the middle cerebral artery territory on the baseline noncontrast brain computed tomography (CT).

Eligible patients who agreed to participate underwent MRI of the brain after their baseline CT scan. Regardless of the MRI results, patients were treated with 0.9mg/kg intravenous tPA (10% bolus over 1 minute, followed by continuous infusion of the remaining dose over 60 minutes) as quickly as possible after their initial MRI scan and no later than 6 hours from the onset of their stroke symptoms. Mismatch profiles and perfusion-weighted imaging (PWI) lesion volumes were not determined before tPA administration. Transcranial Doppler monitoring of thrombolysis was not performed. Repeat MRI scans were obtained 3 to 6 hours after initiation of thrombolytic therapy and at day 30. If neurological deterioration occurred during the hospital stay, an additional CT and/or MRI scan was obtained to document brain hemorrhage. Neurological deficits were evaluated with the NIHSS before tPA therapy, 3 to 6 hours after tPA, and at days 30 and 90. The mRS score was obtained at baseline (prestroke estimate), 30 days, and 90 days. The TOAST (Trial of Org 10172 in Acute Stroke Treatment) stroke subtype classification[20] was performed at 30 days. The 30- and 90-day clinical assessments were performed in person by an individual who was blinded to the patient's MRI profile. Any patient who developed worsening of two or more points on the NIHSS had an urgent CT or MRI scan performed. If any degree of brain hemorrhage was identified, then the imaging studies and clinical data were reviewed by an independent Data Safety and Monitoring Board committee to determine whether the hemorrhage was potentially symptomatic. SICHs were classified by the Data Safety and Monitoring Board committee using the following criteria: "minor SICH" if they were associated with a worsening of 2 or 3 points on the NIHSS within 36 hours of tPA administration, and "major SICH" if associated with a worsening of 4 or more points within 36 hours of tPA administration.

Magnetic Resonance Imaging Protocols/Analysis

MRI scans were obtained on 1.5T scanners equipped with high-performance gradient systems and capable of echo planar imaging. MRI sequence parameters were standardized across centers. The baseline MRI and first follow-up MRI scans included the following sequences: diffusion-weighted imaging (DWI), dynamic susceptibility PWI after a bolus of intravenous gadolinium, three-dimensional time-of-flight magnetic resonance angiography of the intracranial circulation (MRA), conventional T1, and gradient-recalled echo imaging. MRI scans at day 30 included a fluid-attenuated inversion recovery sequence.

To determine PWI lesion volumes, we used in-house developed software based on the algorithm of Ostergaard and colleagues.[20,21] An arterial input function from the proximal middle cerebral artery contralateral to the ischemic lesion was used to generate T_{max} maps using a 2-second delay as the lower threshold indicating hypoperfused brain tissue.[22] T_{max} maps with a 2-second or more delay were used to calculate the PWI lesion volumes.

T_{max} is the maximum of the tissue residue function characteristic to each voxel and reflects how much the tissue response lags behind the stimulus by an arterial input into the voxel and inherently corrects for the length of the gadolinium bolus. T_{max} has been shown to be a sensitive parameter to detect perfusion deficits and tissue destined for infarction.[23]

DWI lesion volumes were calculated using a semiautomated thresholding method to identify regions of interests with high DWI signal intensity (exceeding the DWI signal intensity of the contralateral hemisphere by more than three standard deviations). Apparent diffusion coefficient maps were generated and used to confirm that DWI lesions were new ischemic lesions.

Imaging processing and determination of MRI lesion vol-

umes were performed at the coordinating center by a single reader (V.N.T.) who was blinded to clinical outcomes. An additional blinded reader (W.K.) also determined lesion volumes for all PWI and DWI scans for determining interrater agreement.

Analysis of all MRA images, both the source and the maximum intensity projection images, was performed by a neuroradiologist (M.P.M.) who was blinded to all clinical data except for which side of the brain corresponded with the new neurological symptoms. Scoring of the distal internal carotid, basilar, and the major intracranial arteries of the circle of Willis (middle cerebral artery first branch, anterior cerebral artery first branch, and posterior cerebral artery first branch) was performed as follows: (1) normal, (2) decreased flow, (3) occluded, or (4) technically inadequate. Comparisons with normal contralateral arteries were made, when appropriate, to facilitate scoring. The early follow-up MRAs (3–6 hours after tPA bolus) were compared with the baseline MRA in an unblinded fashion to determine whether partial or complete recanalization had occurred. Complete recanalization was defined as a change from occluded to normal or decreased flow to normal. Partial recanalization was defined as a change from occlusion to decreased flow.

Early reperfusion required a 30% or greater and 10ml or more reduction in PWI lesion volume on the 3- to 6-hour follow-up scan. The "favorable clinical response" rate was defined as the proportion of patients with an NIHSS score of 0 to 1 or 8-point or greater improvement at 30 days. Patients were categorized according to their baseline MRI profile. The "Mismatch" profile was defined as a PWI lesion that was 10ml or more and 120% or more of the DWI lesion. The "Small Lesion" profile was defined as a DWI and PWI volume both less than 10ml (by definition, the presence or absence of reperfusion cannot be assessed in these patients because the baseline PWI lesion is smaller than the minimum reduction in PWI volume required for "reperfusion"). The "No Mismatch" profile was defined as a PWI volume less than 120% of the DWI lesion volume (patients with the Small Lesion profile excluded).

Hypotheses

The DEFUSE study was designed to test the primary hypothesis that tPA-treated patients with a mismatch who had early reperfusion would have a significantly higher rate of "favorable clinical response" than mismatch patients who did not have early reperfusion. In contrast, it was hypothesized that the favorable response rate in patients who did not have a mismatch would not be enhanced by early reperfusion.

A preplanned interim analysis was performed near the midpoint in the study (October 2003) after data from 34 patients were available. This analysis showed that a specific baseline MRI pattern appeared to be associated with severe intracranial hemorrhage and poor outcome after reperfusion. This MRI pattern, which was termed "Malignant profile," was characterized by a large DWI lesion volume and/or a large PWI lesion volume with long delays on the T_{max} map. The malignant profile was empirically defined as a baseline DWI lesion 100ml or more and/or a PWI lesion of 100ml or more with 8 seconds or longer of T_{max} delay. Once this profile was identified, an additional primary hypothesis was added to assess the clinical response to early reperfusion in mismatch patients who did not have the Malignant profile; this group was termed "Target Mismatch."

A secondary end point compared the distribution of 30-day mRS scores in patients who had early reperfusion versus no early reperfusion. An additional analysis compared the rate of favorable clinical response among patients who did or did not experience early recanalization of a symptomatic MRA lesion. The clinical response after early reperfusion was also evaluated for patients with and without a symptomatic MRA lesion on the baseline scan.

Statistical Analysis

Fisher's exact test was used to test the primary hypotheses. Odds ratios for experiencing a favorable clinical response based on reperfusion status were adjusted for baseline imbalances between the reperfusion and no reperfusion groups using multiple logistic regressions for the following predefined factors: age, NIHSS score, stroke onset to treatment time, glucose, DWI volume, and PWI volume. Differences in the distributions of mRS scores were tested with the Mantel–Haenszel statistic. Interrater agreement for classification of mismatch and early reperfusion was assessed with the κ statistic. An intraclass correlation coefficient was used to determine the correlation between the baseline DWI and PWI lesion volume measurements of the two independent observers.

Results

Patient Recruitment and Characteristics

A total of 1,020 patients were screened and 74 patients were enrolled between April 2001 and April 2005. The most common reasons for exclusion were inability to treat within 6 hours (36%), NIHSS score less than 6 (23%), medical contraindications to tPA therapy (9%), treatment with tPA within 3 hours (7%), and CT-documented intracranial hemorrhage or extensive early infarct signs (5%). Inability to obtain an MRI scan was the reason for exclusion in 2%. Of the 74 patients enrolled, each patient successfully underwent an acute MRI scan. The quality of the baseline MRI sequences was sufficient for determination of DWI lesion volume in 100%, PWI volume in 92%, and MRA abnormalities in 92% of scans. MRA scans were of insufficient quality due to patient motion ($n = 6$), and PWI was of insufficient quality due to failure to inject the gadolinium contrast bolus at the appropriate time ($n = 4$) and excessive patient motion ($n = 2$). The κ value for interrater agreement was 0.92 (95% confidence interval [CI], 0.83–1.00) for mismatch and 0.91 (95% CI, 0.80–1.00) for early reperfusion. The intraclass correlation coefficients were 0.98 ($p < 0.001$) for baseline DWI volumes and 0.91 ($p < 0.001$) for baseline PWI volumes. Baseline characteristics of the DEFUSE patients are listed in Table 1. The median time between tPA bolus and performance of the early follow-up MRI was 4 hours and 15 minutes.

Table 1. Baseline Characteristics (n = 74)

Mean age (SD), yr	70.9 (14.6)
White, %	89
Female sex, %	55
Hypertension, %	61
Cardiac disease, %	42
Diabetes mellitus, %	27
Cigarette smoking (current and previous), %	42
Hyperlipidemia, %	24
Prior stroke/TIA, %	15
Median baseline NIHSS score (IQR)	11.5 (8)
Median time to ED arrival (IQR), min	190 (95)
Median time to treatment (IQR), min	328 (40)
Median door-to-needle time (IQR), min	133 (83)
Median DWI lesion volume baseline (IQR), ml	10 (23)
Median PWI lesion volume baseline (IQR), ml[a]	48 (91)
PWI/DWI mismatch at baseline[b]	54% (37/68)
MRA partial or complete occlusion[c]	68% (46/68)

[a]Six patients did not have an interpretable baseline perfusion-weighted imaging (PWI) volume, and thus are excluded from the calculation of baseline PWI volume.

[b]PWI/diffusion-weighted imaging (DWI) mismatch defined as PWI lesion volume ≥120% of DWI lesion volume with a minimum of 10ml of mismatch. Six patients did not have a satisfactory baseline PWI, thus mismatch status could not be determined.

[c]Twenty-two patients did not have a symptomatic lesion identified on the baseline magnetic resonance angiography (MRA). Six patients did not have an interpretable baseline MRA.

SD = standard deviation; TIA = transient ischemic attack; NIHSS = National Institutes of Health Strokes Scale; IQR = interquartile range; ED = emergency department.

Magnetic Resonance Imaging Profiles and Early Reperfusion

In 10 patients, either the baseline MRI profile or the presence or absence of early reperfusion could not be determined because the baseline or follow-up PWI was technically inadequate (Table 2). Among all patients for whom the presence or absence of early reperfusion could be determined (n = 45), early reperfusion occurred in 22 (49%) and was associated with a favorable clinical response in 45% compared with a 35% rate of favorable response in patients who did not have early reperfusion ($p = 0.55$). The rate of early reperfusion was not significantly different between the Mismatch and the No Mismatch groups (53 vs 36%, respectively; $p = 0.49$).

A perfusion/diffusion mismatch was observed in 54% of patients with interpretable baseline PWI (50% of all enrolled patients). In this population, early reperfusion was associated with a favorable clinical response in 56%. When mismatch patients did not have early reperfusion, the favorable clinical response rate was 19% (odds ratio, 5.4; $p = 0.039$; see Tables 2 and 4). Adjustment for baseline imbalances in prognostic characteristics between the early reperfusion and no early reperfusion groups resulted in an increase in the point estimate of the odds ratio for a favorable clinical response after reperfusion (odds ratio, 7.7; see Table 4) in mismatch patients. In contrast, for patients without a mismatch (No Mismatch profile), the clinical outcomes were less favorable for those who had early reperfusion (see Tables 2 and 4 and Fig 2). None of the 4 (0%) No Mismatch profile patients with early reperfusion had a favorable clinical response compared with 5 of 7 (71%) patients who did not have early reperfusion.

The Small Lesion profile occurred in 26% of the study population (n = 19). Patients with this profile typically had favorable clinical outcomes; 74% had a Rankin score of 2 or less at 30 days (see Table 2). Because these patients, by definition, have small or absent perfusion lesions on their baseline MRI (PWI < 10ml), the effect of reperfusion could not be assessed using the reperfusion criterion of a greater than or equal to 10ml reduction in PWI lesion volume. Ten of these 19 patients had neither a DWI or PWI lesion on the baseline scan. The 30-day TOAST stroke subtype classification for the Small Lesion profile patients was as follows: small artery occlusion (n = 7), undetermined cause (n = 7), cardioembolism (n = 2), and large-artery atherosclerosis (n = 2). The final diagnosis for one patient was probable seizure rather than a stroke.

The Target Mismatch profile was present in 33 of the mismatch patients (48% of patients with interpretable baseline PWI and 45% of all enrolled patients). Early reperfusion could be assessed in 31 of these patients (2 had technically inadequate follow-up PWI). Early reperfusion in Target Mismatch patients was associated with a favorable clinical response in 67% (Table 3). When Target Mismatch patients did not have early reperfusion, the favorable clinical response rate was 19% (odds ratio, 8.7; $p = 0.011$; see Table 4). The point estimate of the odds ratio for a favorable clinical response after reperfusion was not appreciably changed after adjustment in the Target Mismatch group (see Table 4). Differences in 30-day mRS scores for Target Mismatch and No Mismatch patients are shown in Figure 2. Target Mismatch patients who had early reperfusion had more favorable clinical outcomes compared with those who did not experience early reperfusion ($p = 0.005$). In contrast, No Mismatch patients with early reperfusion had less desirable mRS outcomes ($p = 0.04$).

The Malignant profile was associated with a low rate of favorable clinical response (1/6 patients; see Table 3). All three patients with this profile who had early reperfusion had a SICH ($p = 0.003$ compared with early reperfusion patients who did not have the Malig-

Table 2. Clinical Outcomes Based on Magnetic Resonance Imaging Profiles and Reperfusion Status

MRI profile	N	Mean Age (yr)	Median Baseline NIHSS Score	Favorable Clinical Response (95% CI)[a]	mRS of 0-2: 30 Days (95% CI)[b]	mRS of 4-6: 30 Days (95% CI)[b]	SICH (95% CI)
Mismatch with early reperfusion	18	79.3	14.5	56%[c](34-75)	50%[c](29-71)	44% (25-66)	22% (9-45)
Mismatch without early reperfusion	16	68.0	13	19% (7-43)	13% (4-36)	75% (50-90)	6.3% (1-28)
No Mismatch with early reperfusion	4	75.3	13	0% (0-49)	25% (5-70)	75% (30-95)	25% (5-70)
No Mismatch without early reperfusion	7	63.0	15	71% (36-92)	71% (36-92)	14% (3-51)	0% (0-35)
Small Lesion profile	19	70.5	8	53% (32-73)	74% (51-88)	21% (9-43)	0% (0-17)
Unsuccessful baseline PWI	6	66.8	15	33% (10-70)	33% (10-70)	33% (10-70)	0% (0-39)
Unsuccessful follow-up PWI	4	62.3	16	25% (46-70)	25% (5-70)	75% (30-95)	25% (5-70)
All patients	74	70.9	11.5	42% (31-53)	46% (35-57)	45% (34-56)	9.5%[d](5-18)

[a]Favorable clinical response was defined as an improvement of 8 points or more in the National Institutes of Health Stroke Scale (NIHSS) score between baseline and 30 days or a score of 0-1 at 30 days.

[b]A modified Rankin Scale (mRS) score of 0-2 indicates no more than slight disability, a score of 4-5 indicates moderately severe or severe disability, and a score of 6 indicates death.

[c]$p < 0.05$ compared with Mismatch without early reperfusion.

[d]Four of the seven symptomatic intracranial hemorrhages (SICHs) were major (associated with a worsening of four or more points on the NIHSS) and three were minor (associated with a worsening of two or three points on the NIHSS).

CI = confidence interval.

nant profile) and all three died. Five of the six Malignant profile patients had a baseline PWI lesion that was larger than the baseline DWI (median difference between baseline PWI and DWI, 80ml) and four met mismatch criteria. Examples of the MRI profiles are shown in Figure 1.

Magnetic Resonance Angiography Results

An interpretable baseline MRA was obtained in 68 of 74 patients. Sixty-eight percent (46/68) had a symptomatic artery occlusion (either complete or partial) at baseline. For 44 of these patients, the presence or absence of early recanalization could be determined (2 of these patients did not have an interpretable early follow-up MRA). Complete early recanalization occurred in 27% and partial recanalization in 16%, for an overall recanalization rate of 43% (Table 5).

In general, patients with MRA-documented early recanalization also had early reperfusion on PWI ($\kappa = 0.58$; $p = 0.001$). There were four patients who had recanalization who did not have reperfusion and three patients who had reperfusion but no recanalization. Patients with early recanalization had a median 74% reduction in the PWI volume obtained 3 to 6 hours after initiation of tPA, compared with a median 7.5% increase if no recanalization occurred ($p < 0.001$). For patients with partial recanalization, the median reduction was 57% compared with 80% in patients with complete recanalization, but the total volume of reperfused tissue was essentially the same (62 ± 46ml for partial and 57 ± 38ml for complete recanalization). Among all patients with a symptomatic vessel occlusion, early recanalization was associated with a 42% rate of favorable clinical response, compared with 28% for those without early recanalization ($p = 0.36$). There was no difference in the clinical outcomes in patients with partial (43% favorable response) versus complete (42% favorable response) recanalization. Patients with the Mismatch pattern at baseline, in whom recanalization could be assessed (n = 28), had a higher rate of favorable clinical response (53%) if early recanalization occurred when compared with Mismatch patients who did not experience early recanalization (8%; $p = 0.016$).

The site of the symptomatic occlusions on the baseline MRA in patients with and without reperfusion was similar (Table 6). When patients with a symptomatic MRA occlusion had early reperfusion, their clinical outcomes tended to be better than when reperfusion did not occur (Table 7). However, this difference did not reach statistical significance (odds ratio, 2.1; 95% CI, 0.47–9.44). Clinical outcomes did not appear to differ, based on the presence or absence of reperfusion, for patients without baseline MRA lesions (odds ratio, 1.1; 95% CI, 0.08–15.51); however, the sample size of this subgroup is small (see Table 7).

Discussion

The DEFUSE study confirmed the primary hypothesis that early reperfusion is associated with a more favorable clinical response in patients with the perfusion/diffusion mismatch profile than in nonmismatch patients. In addition, during the course of the trial, additional MRI profiles were identified that have the potential to refine and enhance the mismatch hypothesis; the Target Mismatch profile appears to identify patients who have an especially robust clinical response rate (67%) after early reperfusion, whereas the Malig-

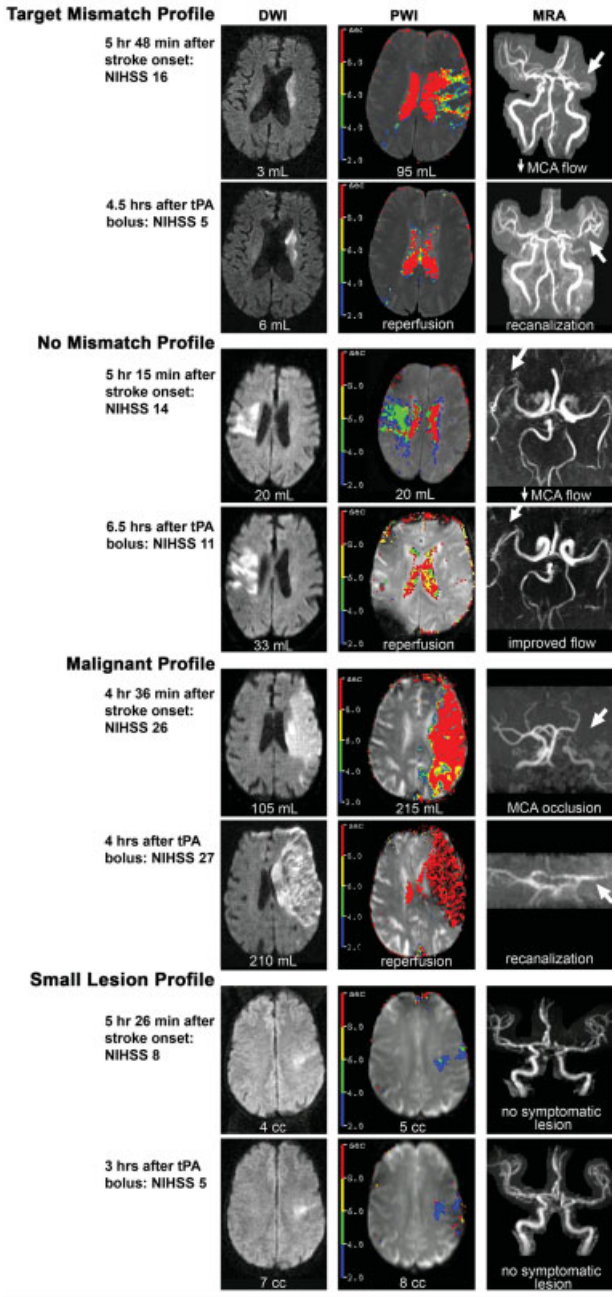

Fig 1. Examples of magnetic resonance imaging (MRI) profiles. Baseline and follow-up diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), and magnetic resonance angiography (MRA) scans for patients with different MRI profiles. Lesion volumes represent the total lesion volume (volumes from each brain slice are summed). The colored scale on the PWI maps indicates the degree of delay (in seconds) of gadolinium arrival relative to the arrival of the arterial input. Color within the ventricles on the PWI maps is an artifact and is not included in the PWI volume. The clinical outcomes of these patients at 30 days were: Target Mismatch profile patient, modified Rankin Scale (mRS) score of 2 and National Institutes of Health Stroke Scale (NIHSS) score of 2; the Malignant profile patient died on hospital day 3 from intracranial hemorrhage; No Mismatch patient, mRS score of 5 and NIHSS score of 11; Small Lesion patient, mRS score of 0 and NIHSS score of 2. tPA = tissue plasminogen activator.

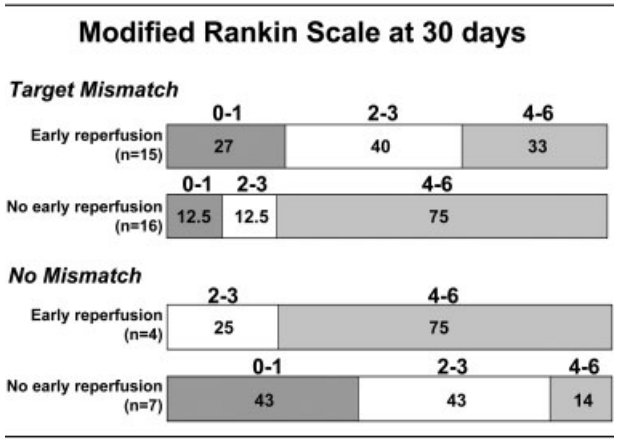

Fig 2. Modified Rankin Scale measurement at 30 days. The statistical comparison of the outcomes was performed with the Mantel–Haenszel test using all seven categories of the modified Rankin Scale (mRS). The p *value is 0.005 for the Target Mismatch group (more favorable outcomes with early reperfusion) and 0.04 for the No Mismatch group (less favorable outcomes with early reperfusion). The mRS score 0–1 indicates no disability, 2–3 slight to moderate disability, 4–5 severe disability, and a score of 6 indicates death.*

nant profile is strongly associated with reperfusion-related brain hemorrhage.

The DEFUSE study is unique in that it is the first prospective multicenter study to perform advanced MRI techniques (including diffusion, quantitative perfusion techniques, MRA, and gradient-recalled echo imaging) before and shortly after the administration of a thrombolytic agent in consecutive patients. DEFUSE is also the first study to demonstrate a differential clinical response after reperfusion among patient subgroups with different MRI profiles.

For the entire patient population, the association between early reperfusion and desirable clinical outcomes was modest and not statistically significant. However, for patients with the Mismatch profile, especially the Target Mismatch profile, there was a strong and highly significant association between early reperfusion and favorable clinical outcomes. This association between early reperfusion and favorable clinical response was not diminished after controlling for baseline imbalances in established predictors of stroke outcome.[24–27] This finding indicates that early reperfusion likely had a substantial favorable influence on clinical outcomes in both the Mismatch and Target Mismatch groups. These data imply that an intervention that leads to a high rate of early reperfusion has the potential to produce substantial clinical benefits for patients with a Mismatch, particularly a Target Mismatch, who are treated in the 3- to 6-hour time window.

For patients who did not have a mismatch, there was no signal of clinical benefit associated with early reperfusion; outcomes on the mRS were actually signifi-

Table 3. Clinical Outcomes in Patients with Target Mismatch and the Malignant Profile

MRI profile	N	Mean Age (yr)	Median Baseline NIHSS Score	Favorable Clinical Response	mRS of 0-2: 30 Days (95% CI)	mRS of 4-6: 30 Days (95% CI)	SICH (95% CI)
Target Mismatch with early reperfusion	15	78.3	14	67%[a](42-84)	60%[a](36-80)	33%[b](15-58)	6.7% (1-30)
Target Mismatch without early reperfusion	16	68.0	13	19% (7-43)	13% (4-36)	75% (50-90)	6.3% (1-28)
Malignant profile	6	68.3	18.5	17% (3-56)	17% (3-56)	83% (34-97)	50% (19-81)

[a]$p \leq 0.01$, [b]$p = 0.03$, compared with Target mismatch without early reperfusion.

NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; SICH = symptomatic intracranial hemorrhage.

Table 4. Odds Ratios for Favorable Clinical Response in Mismatch and Target Mismatch Patients with Early Reperfusion Compared with No Early Reperfusion

MRI Profile	Analysis	OR	95% CI	*p*
Mismatch	Unadjusted	5.4	1.1-25.8	0.039
Mismatch	Adjusted for baseline NIHSS score and baseline PWI[a]	7.7	1.3-44.8	0.022
Target Mismatch	Unadjusted	8.7	1.7-45.2	0.011
Target Mismatch	Adjusted for baseline NIHSS score and baseline PWI[a]	8.6	1.6-46.5	0.012

Favorable clinical response was defined as an improvement of 8 points or more in the National Institutes of Health Stroke Scale (NIHSS) score between baseline and 30 days or a score of 0-1 at 30 days.

[a]Adjustment for age, time to treatment, baseline DWI volume, baseline glucose did not alter the model.
MRI = magnetic resonance imaging; OR = odds ratio; CI = confidence interval; PWI = perfusion-weighted imaging.

cantly worse for patients in this group who experienced early reperfusion compared with no early reperfusion (see Fig 2). However, the small sample size in this subgroup limits the interpretation of these results. We suspect that the small sample size is also responsible for the unsuspected finding of a high rate of favorable clinical response (5/7) among the No Mismatch patients who did not experience reperfusion. A couple of patients moving from favorable to unfavorable outcome in this group could dramatically affect the outcome rates for this small group. A follow-up study is planned to further evaluate the benefits and risks of early reperfusion in patients without a mismatch.

The Malignant profile was associated with a high risk for fatal SICH in patients who had early recanalization/reperfusion. These patients typically had a large mismatch between the baseline DWI and PWI volumes, a characteristic that has been previously

Table 5. Early Recanalization of Symptomatic Arterial Lesions on Baseline Magnetic Resonance Angiography

Recanalization Status	Lesion Site	Number of Patients
Recanalization: 43% (19/44)		
Complete: 27% (12/44)	Isolated MCA lesion	9
	Tandem MCA/ICA lesion	2
	Isolated ICA lesion	0
	Isolated PCA lesion	1
Partial: 16% (7/44)	Isolated MCA lesion	2
	Tandem MCA/ICA lesion[a]	5
	Isolated ICA lesion	0
	Isolated PCA lesion	0
No recanalization: 57% (25/44)	Isolated MCA lesion	12
	Tandem MCA/ICA lesion[b]	11
	Isolated ICA lesion	1
	Isolated PCA lesion	1

[a]One patient also had an anterior cerebral artery lesion and one had additional lesions in the anterior cerebral and posterior cerebral arteries.

[b]Five patients also had an anterior cerebral artery lesion, one had additional lesions in the anterior cerebral and posterior cerebral arteries, two had additional lesions in the posterior cerebral arteries, and one had additional lesions in the anterior cerebral, posterior cerebral, and basilar artery.
MCA = middle cerebral artery; ICA = internal carotid artery; PCA = posterior cerebral artery.

Table 6. Magnetic Resonance Angiography Findings Based on Magnetic Resonance Imaging Profiles and Reperfusion

MRI profile	Normal	ICA	ICA/MCA[a]	MCA	PCA	Uninterpretable	Total
Mismatch with early reperfusion	3	0	5	8	0	2	18
Mismatch without early reperfusion	2	0	6	8	0	0	16
No mismatch with early reperfusion	1	0	2	1	0	0	4
No mismatch without early reperfusion	3	0	0	3	0	1	7
Small Lesion profile	12	1	2	1	1	2	19
Unsuccessful PWI	1	0	3	4	1	1	10
Total	22	1	18	25	2	6	74

[a]Some patients had additional vessel occlusions (see Table 5).

ICA = isolated lesion of the internal carotid; ICA/MCA = a tandem lesion involving the internal carotid and middle cerebral artery; MCA = an isolated lesion of the middle cerebral artery; PCA = an isolated lesion of the posterior cerebral artery.

thought to identify patients who are likely to benefit from reperfusion therapies.[8,9,11,12,16,28,29] We suspect that the large volume of severe ischemic brain and microvascular injury in these patients substantially increases the risk for reperfusion-related cerebral edema/brain hemorrhage. This concept is supported by a recent study that demonstrated an association between severe perfusion abnormalities and SICH after thrombolysis-induced reperfusion.[30] In conjunction with the DEFUSE data, these findings imply that exclusion of patients with unfavorable imaging profiles could improve the safety and efficacy of reperfusion therapies.

Data regarding the rates of early recanalization achieved after intravenous tPA are sparse, and the relations between early recanalization, early reperfusion, and clinical outcomes have not previously been demonstrated. The DEFUSE data demonstrate that MRA-documented early recanalization is associated with both early reperfusion and favorable clinical outcomes in mismatch patients. However, the rates of early recanalization, particularly complete recanalization, are modest after intravenous tPA therapy. Newer interventional neuroradiological approaches, such as mechanical thrombectomy and intraarterial thrombolysis, may provide higher rates of recanalization/reperfusion than intravenous thrombolysis. [31–33]

As expected, patients without a symptomatic MRA

Table 7. Clinical Outcomes Based on Baseline Magnetic Resonance Angiography Findings and Reperfusion Status

MRA Findings	N	Mean Age (yr)	Median Baseline NIHSS score	Favorable Clinical Response	mRS 0-2: 30 Days	mRS 4-6: 30 Days	SICH
MRA lesion with early reperfusion	16	78.4	14	38% (6/16)	44% (7/16)	50% (8/16)	25% (4/16)
MRA lesion without early reperfusion	17	66.0	13	24% (4/17)	24% (4/17)	65% (11/17)	6% (1/17)
MRA lesion with baseline PWI <10ml	5	64.6	8	40% (2/5)	80% (4/5)	20% (1/5)	0% (0/5)
No MRA lesion with early reperfusion	4	77.5	8.5	75% (3/4)	75% (3/4)	15% (1/4)	0% (0/4)
No MRA lesion without early reperfusion	5	64.8	9	60% (3/5)	60% (3/5)	20% (1/5)	0% (0/5)
No MRA lesion with baseline PWI <10ml	12	72.6	9	58% (7/12)	75% (9/12)	17% (2/12)	0% (0/12)
Unsuccessful baseline MRA	5	78.4	17	60% (3/5)	20% (1/5)	80% (4/5)	20% (1/5)
Unsuccessful baseline or follow-up PWI[a]	10	65.0	15	30% (3/10)	30% (3/10)	50% (5/10)	10% (1/10)

[a]One of these patients had no baseline magnetic resonance angiography (MRA) lesion and one had an unsuccessful baseline MRA.

NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; SICH = symptomatic intracranial hemorrhage; PWI = perfusion-weighted imaging.

lesion on the baseline scan had lower baseline NIHSS scores and had generally favorable outcomes. Among patients with symptomatic MRA lesions at baseline, early reperfusion was associated with a slightly higher rate of favorable clinical response. However, there was no statistical evidence that clinical outcomes after early reperfusion were modified by the presence or absence of a symptomatic baseline MRA lesion. Therefore, the DEFUSE data imply that selecting patients for reperfusion therapy based on favorable PWI/DWI profiles may be superior to a strategy that relies on MRA data alone.

Some patients with small baseline PWI and DWI lesions likely had small deep perforating vessel occlusions. Others may have experienced spontaneous recanalization before the baseline MRI study. It is not possible to accurately assess the effects of early reperfusion with MRI in these patients because PWI and MRA do not have adequate sensitivity to document reperfusion or recanalization of very small lesions. Further study is required to clarify whether patients with small baseline PWI and DWI lesions benefit from reperfusion therapies.

The DEFUSE study was not designed to demonstrate the efficacy of intravenous tPA. The absence of a placebo control group precludes conclusions regarding the benefits or risks of tPA therapy. The small number of patients in the No Mismatch group limits our ability to characterize the response to reperfusion in this subgroup. The Target Mismatch profile and the Malignant profile were defined during the course of the trial; the predictive values of these MRI profiles should be confirmed in an independent patient sample. Door-to-needle times were longer than optimal, in part related to the protocol requirement to obtain both CT and MRI before treatment. Recent studies have demonstrated that MRI alone is adequate to exclude intracranial hemorrhage before thrombolysis.[34,35]

The DEFUSE results demonstrate that acute MRI scans are feasible in acute ischemic stroke patients at selected centers, and that MRI findings appear to differentiate patient subgroups that will benefit from therapies that lead to early reperfusion from those who are unlikely to benefit or may be harmed. These findings have important implications for the design of future trials of reperfusion therapies in extended time windows.

The PWI analysis software used for this study was based on the UCLA neuroimaging analysis program developed by Jeffry Alger, Chelsea Kidwell and Jeff Saver.

The DEFUSE study was supported by the NIH (National Institute on Neurological Disorders and Stroke, RO1 NS39325, G.W.A., M.P.M., M.M.; K24 NS044848, G.W.A.).

tPA was supplied at no charge by Genentech (US and Canada sites) and Boehringer Ingelheim (Belgium site). Neither Genentech, Boehringer Ingelheim, nor the NIH played a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation or approval of the manuscript.

Gregory W. Albers had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix

DEFUSE investigators: Stanford University—Gregory Albers, MD, Roland Bammer, PhD, Anna Finley Caulfield, MD, Wataru Kakuda, MD, Stephanie Kemp, BS, Maarten Lansberg, MD, Michael Marks, MD, Michael Moseley, PhD, Neil Schwartz, MD, Christine Wijman, MD; University of Pittsburgh—Lawrence Wechsler, MD, Sharon DeCesare; Beth Israel Deaconess—Gottfried Schlaug, MD, Cheryl Hogan; University of Gasthuisberg—Vincent Thijs, MD, Ingeborg Wauters, RN; University of Utah—Elaine Skalabrin, MD, Janet Woodruff, RN; University of Alberta—Ashfaq Shuaib, MD, Brenda Schwendt, RN; Wayne State University—William Coplin, MD, Flicia Mada, RN.

Data Safety Monitoring Board: Jeffrey Saver, MD, Pierre Fayad, MD, Janet Wilterdink, MD, Scott Hamilton, PhD.

References

1. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333:1581–1587.
2. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363:768–774.
3. Zweifler RM, Brody ML, Graves GC, et al. Intravenous t-PA for acute ischemic stroke: therapeutic yield of a stroke code system. Neurology 1998;50:501–503.
4. Clark WM, Albers GW, Madden KP, Hamilton S. The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. Thrombolytic Therapy in Acute Ischemic Stroke Study investigators. Stroke 2000;31:811–816.
5. Clark WM, Wissman S, Albers GW, et al. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. JAMA 1999; 282:2019–2026.
6. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA 1995;274:1017–1025.
7. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;352:1245–1251.
8. Hacke W, Albers G, Al-Rawi Y, et al. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. Stroke 2005;36:66–73.
9. Thomalla G, Schwark C, Sobesky J, et al. 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. Stroke 2006;37:852–858.

10. Thijs VN, Adami A, Neumann-Haefelin T, et al. Relationship between severity of MR perfusion deficit and DWI lesion evolution. Neurology 2001;57:1205–1211.
11. Parsons MW, Barber PA, Chalk J, et al. Diffusion- and perfusion-weighted MRI response to thrombolysis in stroke. Ann Neurol 2002;51:28–37.
12. Butcher KS, Parsons M, MacGregor L, et al. Refining the perfusion-diffusion mismatch hypothesis. Stroke 2005;36: 1153–1159.
13. Neumann-Haefelin T, Wittsack H-J, Wenserski F, et al. Diffusion- and perfusion-weighted MRI: the DWI/PWI mismatch region in acute stroke. Stroke 1999;30:1591–1597.
14. Nighoghossian N, Hermier M, Adeleine P, et al. Baseline magnetic resonance imaging parameters and stroke outcome in patients treated by intravenous tissue plasminogen activator. Stroke 2003;34:458–463.
15. Schellinger PD, Jansen O, Fiebach JB, et al. Monitoring intravenous recombinant tissue plasminogen activator thrombolysis for acute ischemic stroke with diffusion and perfusion MRI. Stroke 2000;31:1318–1328.
16. Rother J, Schellinger PD, Gass A, et al. Effect of intravenous thrombolysis on MRI parameters and functional outcome in acute stroke <6 hours. Stroke 2002;33:2438–2445.
17. Zivin JA. Perfusion-weighted imaging/diffusion-weighted imaging mismatch on MRI can now be used to select patients for recombinant tissue plasminogen activator beyond 3 hours: con. Stroke 2005;36:1099–1100.
18. Rivers CS, Wardlaw JM, Armitage PA, et al. Do acute diffusion- and perfusion-weighted MRI lesions identify final infarct volume in ischemic stroke? Stroke 2006;37:98–104.
19. Keir SL, Wardlaw JM. Systematic review of diffusion and perfusion imaging in acute ischemic stroke. Stroke 2000;31: 2723–2731.
20. Ostergaard L, Sorensen AG, Kwong KK, et al. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part II: experimental comparison and preliminary results. Magn Reson Med 1996;36:726–736.
21. Ostergaard L, Weisskoff RM, Chesler DA, et al. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part I: mathematical approach and statistical analysis. Magn Reson Med 1996;36:715–725.
22. Thijs VN, Somford DM, Bammer R, et al. Influence of arterial input function on hypoperfusion volumes measured with perfusion-weighted imaging. Stroke 2004;35:94–98.
23. Shih LC, Saver JL, Alger JR, et al. Perfusion-weighted magnetic resonance imaging thresholds identifying core, irreversibly infarcted tissue. Stroke 2003;34:1425–1430.
24. Lu M, Lyden PD, Brott TG, et al. Beyond subgroup analysis: improving the clinical interpretation of treatment effects in stroke research. J Neurosci Methods 2005;143:209–216.
25. Generalized efficacy of t-PA for acute stroke: subgroup analysis of the NINDS t-PA Stroke Study. Stroke 1997;28:2119–2125.
26. Brown DL, Johnston KC, Wagner DP, Haley EC Jr. Predicting major neurological improvement with intravenous recombinant tissue plasminogen activator treatment of stroke. Stroke 2004; 35:147–150.
27. Wechsler LR, Roberts R, Furlan AJ, et al. Factors influencing outcome and treatment effect in PROACT II. Stroke 2003;34: 1224–1229.
28. Albers GW. Expanding the window for thrombolytic therapy in acute stroke. The potential role of acute MRI for patient selection. Stroke 1999;30:2230–2237.
29. Fisher MD, Prichard JW, Warach S. New magnetic resonance techniques for acute ischemic stroke. JAMA 1995;274: 908–911.
30. Alsop DC, Makovetskaya E, Kumar S, et al. Markedly reduced apparent blood volume on bolus contrast magnetic resonance imaging as a predictor of hemorrhage after thrombolytic therapy for acute ischemic stroke. Stroke 2005;36:746–750.
31. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA 1999;282:2003–2011.
32. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of Mechanical Embolectomy in Acute Ischemic Stroke: results of the MERCI trial. Stroke 2005;36:1432–1438.
33. The IMS Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. Stroke 2004;35:904–911.
34. Fiebach JB, Schellinger PD, Gass A, et al. Stroke magnetic resonance imaging is accurate in hyperacute intracerebral hemorrhage: a multicenter study on the validity of stroke imaging. Stroke 2004;35:502–506.
35. Kidwell CS, Chalela JA, Saver JL, et al. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA 2004;292:1823–1830.