The MRA-DWI Mismatch Identifies Patients With Stroke Who Are Likely to Benefit From Reperfusion

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Background and Purpose—The aim of this exploratory analysis was to evaluate if a combination of MR angiography (MRA) and diffusion-weighted imaging (DWI) selection criteria can be used to identify patients with acute stroke who are likely to benefit from early reperfusion.

Methods—Data from DEFUSE, a study of 74 patients with stroke who received intravenous tissue plasminogen activator in the 3- to 6-hour time window and underwent MRIs before and approximately 4 hours after treatment were analyzed. The MRA–DWI mismatch model was defined as (1) a DWI lesion volume less than 25 mL in patients with a proximal vessel occlusion; or (2) a DWI lesion volume less than 15 mL in patients with proximal vessel stenosis or an abnormal finding of a distal vessel. Favorable clinical response was defined as an improvement on the National Institutes of Health Stroke Scale score of at least 8 points between baseline and 30 days or a National Institutes of Health Stroke Scale score ≤1 at 30 days.

Results—Twenty-seven of 62 patients (44%) had an MRA-DWI mismatch. There was a differential response to early reperfusion based on MRA-DWI mismatch status. Reperfusion was associated with an increased rate of a favorable clinical response in patients with an MRA-DWI mismatch (OR, 12.5; 95% CI, 1.8 to 83.9) and a lower rate in patients without mismatch (OR, 0.2; 95% CI, 0.0 to 0.8).

Conclusions—The MRA-DWI mismatch model appears to identify patients with stroke who are likely to benefit from reperfusion therapy administered in the 3- to 6-hour time window after symptom onset. The criteria established for the MRA-DWI mismatch model in this study require validation in an independent cohort. (Stroke. 2008;39:2491-2496.)

Key Words: MRI stroke thrombolysis

Stroke trials have failed to show a significant benefit of intravenous tissue plasminogen activator (tPA) when administered beyond 3 hours. This is the result of an overall decrease in the efficacy of tPA with longer symptom onset-to-treatment times.1 However, there is evidence that even at later treatment times, carefully selected patients may benefit from reperfusion.2 To optimize the efficiency and safety of a trial aimed at restoring blood flow beyond the 3-hour time window, patient subgroups that are most likely to benefit should be included. The perfusion–diffusion mismatch model, based on a mismatch between the lesion volumes on perfusion-weighted MRI (PWI) and diffusion-weighted MRI (DWI), has been proposed as a method to select patients with stroke for reperfusion therapy beyond 3 hours.3–4 A limitation of this model is the requirement to obtain an accurate assessment of the PWI lesion volume in the acute setting. This poses a challenge, because PWI methodology is not well standardized.5 Despite theoretical evidence, it is still controversial whether or not the use of a deconvolution technique for postprocessing of PWI data provides additional clinically relevant data.6–8 Also, there is no consensus regarding which PWI parameter such as mean transit time, time-to-peak of the tissue residue function, or time-to-peak provides optimal sensitivity and specificity for delineating regions of abnormal perfusion and which thresholds should be applied to these maps.5 Finally, it is uncertain whether PWI lesion volumes should be assessed quantitatively or if it is sufficient to visually estimate lesion volumes for the purpose of determining the presence of a PWI-DWI mismatch.

The clinical–diffusion mismatch model, based on a discrepancy in the degree of clinical deficits measured on the National Institutes of Health Stroke Scale (NIHSS) score compared with the lesion volume on DWI, has been proposed as an alternative method that does not rely on PWI to select patients for thrombolysis.9 However, a previous study by our group demonstrated that this method may be less powerful...
than the PWI-DWI mismatch model for identifying optimal candidates for reperfusion therapy. Because the target of thrombolytic therapy is a thromboembolic occlusion of a cerebral vessel, optimal selection criteria for thrombolytic therapy may be based on the presence of a vessel occlusion or stenosis and the absence of a large territory of irreversible injury. The aim of this study is to evaluate a novel model based on MR angiography (MRA) and DWI, the “MRA-DWI mismatch,” for identifying patients who are likely to benefit from tPA in the 3- to 6-hour time window. We hypothesize that patients with an intracranial vessel stenosis or occlusion on MRA and a relatively small DWI lesion (MRA-DWI mismatch) are most likely to benefit from early reperfusion.

Materials and Methods
The study is a post hoc exploratory analysis using data from the Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE) study. Details of DEFUSE have been described previously. Briefly, this was a multicenter, open-label study of intravenous tPA administered in the 3- to 6-hour time window. Patients underwent an MRI, including PWI, DWI, and MRA, before and 3 to 6 hours after tPA administration. The MRA was a flow-compensated 3-dimensional time-of-flight of the circle of Willis. Scan parameters were as follows: flip angle=20°, TR/TE=34 ms/minimum, number of excitations=1, field of view=240 mm, rectangular field of view=75%, slice thickness=1 mm interpolated to 0.5 mm, number of slices 116, acquisition matrix=512×128 interpolated to 512×512, receiver bandwidth=±32 kHz. To increase blood–tissue contrast enhancement, the time-of-flight sequence was enhanced by magnetization transfer prepulses. Further blood–tissue contrast enhancement by consideration of saturation effects from slow-flowing blood and multiple radiofrequency excitation was achieved by breaking the 3-dimensional slab into 2 smaller overlapping volumes (12 slices) and using a ramped excitation pulse with increasing flip angle in a distal direction. Because of inclusion of different vendors, slight variations of the MRA protocol across centers were allowed. The PWI was a dynamic gradient-echo single-shot echoplanar image (TE=60 ms, TR=2 seconds, 128×128 matrix) sequence repeated 40 times during the passage of a single dose of Gd-DTPA bolus followed by a 20-mL saline chaser. All patients were treated with tPA regardless of the findings on their baseline MRI.

The MRA was rated independently by an experienced neuroradiologist (M.P.M.) and stroke neurologist (J.M.O.) on the following scale. For the terminal internal carotid artery and first segment of the middle cerebral artery: 1=normal; 2=20% reduced flow; 3=occlusion. For the anterior cerebral artery, posterior cerebral artery, and the second division of the middle cerebral artery: 1=normal; 2=abnormal. Raters were aware of the symptomatic hemisphere at the time of their MRA rating but were blinded to all other imaging and clinical data. If the MRA interpretation differed between the 2 readers, a consensus was reached in a joint reading. Degree of recanalization was rated on a 3-point scale calculated by subtracting the follow-up MRA score from the baseline MRA score. PWI lesion volumes were determined on time-to-peak maps that were generated according to the Ostergaard method with the arterial input function selected from the contralateral cerebral artery. Semiautomated thresholding was used to identify hyperperfused tissue defined as a delay of at least 2 seconds on the time-to-peak map. The DWI lesion volume was assessed by a semiautomated procedure to include pixels with a signal intensity of at least 3 SDs above the signal intensity of a comparable region in the contralateral hemisphere. According to prespecified DEFUSE criteria, “favorable clinical response” was defined as an improvement on the NIHSS score of at least 8 points between baseline and 30 days or a NIHSS score ≤1 at 30 days, and the PWI-DWI mismatch as a PWI lesion volume that exceeded the DWI lesion volume by >20% and >10 mL. Reperfusion was defined as a reduction in PWI lesion volume of at least 30% between the baseline and follow-up MRI scan. For the primary analysis, MRA-DWI mismatch was prespecified as an MRA score of 3 and a DWI lesion volume less than 25 mL or an MRA score of 2 and a DWI lesion volume less than 15 mL. Several alternative definitions for the MRA-DWI mismatch, based on different MRA score and DWI lesion volume cutoffs, were explored as secondary analyses. These included: (1) limiting the mismatch definition to include only patients with an MRA score of 3; (2) having a more stringent DWI volume cutoff of 15 mL for patients with an MRA score of 3; and (3) including all patients with an MRA lesion regardless of DWI lesion volume. Agreement between the MRA-DWI mismatch and the PWI-DWI mismatch models for selecting mismatch patients was evaluated. The ability of the MRA-DWI mismatch model to select patients who are likely to benefit from reperfusion was assessed by determining the OR of a favorable clinical response associated with reperfusion in patients with a MRA-DWI mismatch. As a secondary analysis, the association between recanalization and favorable clinical response rates was assessed in patients with MRA-DWI mismatch and in patients without mismatch.

Continuous variables were compared using t tests, ordinal variables using the Mann-Whitney U test, and categorical variables using χ² or Fisher exact tests. ORs for favorable clinical response were calculated from 2×2 tables and, when appropriate, adjusted for imbalances in baseline variables using logistic regression. All statistical analyses were performed using SPSS 13.0 for Windows (SPSS Inc, Chicago, Ill) and results were deemed significant at a probability value of 0.05.

Results
DEFUSE enrolled 74 patients. This substudy is limited to the 62 patients with an adequate quality DWI, PWI, and MRA at baseline for whom PWI-DWI mismatch and MRA-DWI mismatch could be determined. Six patients were excluded because of poor MRA quality, 5 because of poor PWI quality, and one because of poor MRA and PWI quality. Forty-one of the 62 included patients had a lesion on MRA in the symptomatic hemisphere: one internal carotid artery occlusion, 38 middle cerebral artery occlusions, and 2 posterior cerebral artery occlusions.

MRA-DWI mismatch was present in 27 of the 62 patients (44%; 95% CI, 32% to 56%). Patients with MRA-DWI mismatch had smaller DWI lesion volumes and were treated later than patients without mismatch. Otherwise, the baseline characteristics were similar between these groups (Table 1). PWI-DWI mismatch was present in 34 of 62 patients (55%; 95% CI, 43% to 67%). Agreement in terms of mismatch classification between the MRA-DWI mismatch model and the PWI-DWI mismatch model was 63% (95% CI, 50% to 74%; Table 2). In 5 patients, reperfusion status could not be determined because of a poor-quality follow-up perfusion scan. Therefore, analyses of the effects of reperfusion were limited to the 57 patients with adequate baseline and follow-up PWI data. Early reperfusion occurred in 9 of the 27 patients (33%; 95% CI, 19% to 52%) with an MRA-DWI mismatch and 14 of 30 patients (47%; 95% CI, 30% to 64%) without a mismatch (P=nonsignificant). MRA-DWI mismatch patients with reperfusion were older (78±10 years) than MRA-DWI mismatch patients without reperfusion (65±18 years; P=0.02). Otherwise, the baseline characteristics were similar between these 2 groups (Table 1). Patients without MRA-DWI mismatch who reperfused were also older than their counterparts who did not reperfuse. In addition, they showed a trend toward having worse NIHSS...
scores and larger DWI and PWI lesion volumes (Table 1). Reperfusion was associated with an increased rate of a favorable clinical response in MRA-DWI mismatch patients (OR, 12.3; 95% CI, 1.8 to 84.0): 7 of 9 patients with reperfusion had a favorable clinical response compared with 4 of 18 patients without reperfusion. In contrast, reperfusion was associated with a decreased rate of a favorable clinical response in patients without an MRA-DWI mismatch (OR, 0.2; 95% CI, 0.0 to 0.8): 3 of 14 patients with reperfusion had a favorable clinical response compared with 10 of 16 without reperfusion. After adjustment for imbalances in baseline characteristics, the association between reperfusion and favorable clinical response in patients without an MRA-DWI mismatch attenuated (OR, 0.3; 95% CI, 0.0 to 1.9) and was no longer significant (P=0.2).

Similar to the results based on reperfusion status, recanalization of the symptomatic MRA lesion was also associated with an increased rate of favorable clinical response in MRA-DWI mismatch patients; in this group, the favorable clinical response rate increased from 29% in patients with no evidence of recanalization, to 43% in patients with a 1-point improvement in their MRA between baseline and follow-up, and to 100% in patients with a 2-point improvement in their MRA (P=0.04). In contrast, recanalization was not associated with a favorable clinical response in patients without an MRA-DWI mismatch (P=0.51).

Table 3 summarizes how MRA-DWI mismatch models with varying MRA and DWI selection criteria perform for identifying patients who are likely to benefit from reperfusion. The performance of the PWI-DWI mismatch model is also included in Table 3 (Model H) for comparison purposes. Of the several alternative MRA-DWI mismatch definitions evaluated, the strongest association between reperfusion and favorable clinical response was observed when MRA-DWI mismatch was defined more stringently as an MRA score of 2 or 3 and a DWI lesion volume <15 mL (OR, 26.0; 95% CI, 2.2 to 304.7; Table 3, Model C). Conversely, with less stringent criteria such as patients selected based on the presence of an MRA lesion alone (regardless of the DWI lesion volume), reperfusion was not significantly associated with an increased chance of favorable response (Table 3, Models F and G).

Discussion
This study suggests that in patients with stroke who present between 3 and 6 hours after symptom onset, a combination of MRA and DWI findings can identify a subgroup of patients who likely benefit from early reperfusion. The MRI pattern observed in these patients consists of a relatively small DWI lesion in combination with MRA evidence of an intracranial vessel stenosis or occlusion. This pattern, referred to as the MRA-DWI mismatch, may provide an alternative for the PWI-DWI mismatch to select patients who are good candidates for acute stroke trials aimed at restoring blood flow in the 3- to 6-hour time window. The exploratory nature of this analysis and the relatively small number of subjects included in the study, however, necessitate validation of the MRA-DWI mismatch model in an external data set. A DEFUSE follow-up study is being planned for this purpose. If the MRA-DWI mismatch model is validated, it could be used for patient selection in a Phase III randomized trial of

Table 1. Baseline Characteristics of Patients With and Without MRA-DWI Mismatch

<table>
<thead>
<tr>
<th>Variable</th>
<th>MRA-DWI Mismatch</th>
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<tr>
<td></td>
<td>Reperfusion (n=8)</td>
<td>No (n=19)</td>
<td>All (n=27)</td>
<td>Reperfusion (n=14)</td>
<td>No (n=16)</td>
<td>All (n=30)*</td>
<td></td>
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<tr>
<td>Mean age (SD), yr</td>
<td>78 (9)</td>
<td>65 (17)†</td>
<td>69 (16)</td>
<td>79 (7)</td>
<td>66 (16)†</td>
<td>72 (14)</td>
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<tr>
<td>Mean glucose (SD), mg/dL</td>
<td>169 (82)</td>
<td>138 (55)</td>
<td>148 (65)</td>
<td>128 (47)</td>
<td>144 (70)</td>
<td>136 (60)</td>
<td></td>
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<tr>
<td>Mean time to treatment (SD), min</td>
<td>337 (41)</td>
<td>335 (24)</td>
<td>336 (30)</td>
<td>299 (35)</td>
<td>321 (38)</td>
<td>311 (38)†</td>
<td></td>
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<tr>
<td>Mean systolic blood pressure (SD), mm Hg</td>
<td>139 (13)</td>
<td>152 (24)</td>
<td>148 (22)</td>
<td>156 (18)</td>
<td>149 (20)</td>
<td>152 (19)</td>
<td></td>
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<tr>
<td>Mean diastolic blood pressure (SD), mm Hg</td>
<td>73 (13)</td>
<td>81 (12)</td>
<td>79 (13)</td>
<td>75 (18)</td>
<td>76 (15)</td>
<td>76 (16)</td>
<td></td>
<td></td>
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<tr>
<td>Median NIHSS score (IQR)</td>
<td>12 (6)</td>
<td>10.5 (6.25)</td>
<td>11 (7)</td>
<td>14 (12.5)</td>
<td>9 (8)</td>
<td>11 (8)</td>
<td></td>
<td></td>
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<tr>
<td>Mean PWI lesion volume, mL</td>
<td>63 (39)</td>
<td>63 (80)</td>
<td>63 (68)</td>
<td>82 (67)</td>
<td>39 (62)</td>
<td>59 (67)</td>
<td></td>
<td></td>
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<tr>
<td>Mean DWI lesion volume, mL</td>
<td>8 (7)</td>
<td>6 (6)</td>
<td>7 (6)</td>
<td>41 (34)</td>
<td>21 (34)</td>
<td>30 (35)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, % female</td>
<td>78%</td>
<td>44%</td>
<td>56%</td>
<td>36%</td>
<td>56%</td>
<td>47%</td>
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MRA-DWI mismatch defined as an MRA score of 2 and a DWI lesion volume <15 mL or an MRA score of 3 and a DWI lesion volume <25 mL. PWI-DWI mismatch, defined as a PWI lesion volume that exceeds the DWI lesion volume by at least 20% and at least 10 mL.

Discussion
This study suggests that in patients with stroke who present between 3 and 6 hours after symptom onset, a combination of MRA and DWI findings can identify a subgroup of patients who likely benefit from early reperfusion. The MRI pattern observed in these patients consists of a relatively small DWI lesion in combination with MRA evidence of an intracranial vessel stenosis or occlusion. This pattern, referred to as the MRA-DWI mismatch, may provide an alternative for the PWI-DWI mismatch to select patients who are good candidates for acute stroke trials aimed at restoring blood flow in the 3- to 6-hour time window. The exploratory nature of this analysis and the relatively small number of subjects included in the study, however, necessitate validation of the MRA-DWI mismatch model in an external data set. A DEFUSE follow-up study is being planned for this purpose. If the MRA-DWI mismatch model is validated, it could be used for patient selection in a Phase III randomized trial of
remain significant. We hypothesize that tPA treatment did not reperfusion and favorable outcome attenuated and did not ter adjustment for these imbalances, the association between volumes than no-mismatch patients without reperfusion. Af-

NIHSS scores, and larger baseline PWI and DWI lesion characteristics that are associated with stroke outcome11–14; no-mismatch patients with reperfusion were older, had higher NIHSS scores, and larger baseline PWI and DWI lesion volumes than no-mismatch patients without reperfusion. Af-

ther adjustment for these imbalances, the association between reperfusion and favorable outcome attenuated and did not remain significant. We hypothesize that tPA treatment did not play a significant role (either favorable or unfavorable) in the clinical outcome of no-mismatch patients. Consequently, we suspect that excluding no-mismatch patients from a study aimed at restoring perfusion will likely increase the power of the study. It is however theoretically possible that the high rate of favorable outcome in patients without mismatch who did not reperfuse based on PWI lesion volume measurement was related to improvements in tissue microperfusion or some other benefit of tPA, which is not detectable with current PWI technology. To definitively assess the benefits and risks of tPA in mismatch versus no-mismatch patients would require a randomized trial.

The main advantage of using an MRA-based mismatch model over a PWI-based mismatch model is the relative ease of obtaining and visually analyzing MRA lesions compared with PWI lesions. This study used a simple 3-point scoring system to rate MRA lesions. The MRAs were standard 3-dimensional time-of-flight images of the circle of Willis that can be generated in approximately 2 to 3 minutes.15 In contrast, the PWI volumetric lesion analysis used in this study was more time-consuming because it required postprocessing of the PWI images on a separate workstation using a deconvolution technique and a semiautomated method for computing the first moment of the tracer uptake curve that can be generated in approximately 2 to 3 minutes.15 In contrast, the PWI volumetric lesion analysis used in this study was more time-consuming because it required postprocessing of the PWI images on a separate workstation using a deconvolution technique and a semiautomated method for quantifying the lesion volume.

There are, however, methods available to simplify the PWI image analysis. These include using PWI maps derived by deconvolution of the arterial input function and visually comparing the PWI lesion volume with the DWI
lesion volume to determine whether a mismatch is present instead of measuring DWI and PWI lesion volumes using image analysis software. The recent trials of desmoteplase for treatment of acute stroke in the 3- to 9-hour time window (DIAS and DEDAS) are examples of studies that relied on a visual assessment of PWI and DWI maps to determine whether a mismatch is present. Visual readings, however, may not correspond well with quantitative analysis of lesion volumes. For instance, in DEDAS, the existence of a mismatch was overestimated in 16% (6 of 37). Whether the increased accuracy that can be achieved with the quantitative PWI analysis is clinically relevant has yet to be established.

Another potential advantage of the use of MRA over PWI is that it obviates the need for gadolinium contrast, an agent that recently has been associated with the development in rare instances of nephrogenic systemic fibrosis in patients with severe renal insufficiency or those on hemodialysis. The US Food and Drug Administration currently recommends that MRI contrast should be used only if clearly necessary in patients with advanced kidney failure. Although the use of contrast seems clearly justifiable if it is needed to determine whether a patient with acute stroke is eligible for thrombolytic therapy, time delays may be introduced at centers that require assessment of renal function before scanning.

This study is unique in that it evaluates the effect of early reperfusion in patients with and without an MRA-DWI mismatch. One previous study evaluated the relationship between PWI-DWI mismatch and MRA changes, but differed from ours in 2 important ways. First, the potential benefit of early reperfusion could not be assessed because follow-up MRIs were obtained at later times; and second, MRA findings were studied in isolation as opposed to a combined assessment of MRA and DWI findings into a single MRA-DWI mismatch model. In our study, selection of patients based on MRA criteria alone without specific DWI lesion criteria yielded no significant association between reperfusion and favorable clinical response. This suggests that the MRA profile alone is not optimal for identifying patients who respond favorably to reperfusion. This may be explained by inclusion of patients with vessel occlusions and relatively large DWI lesions who have limited or no salvageable brain tissue and thus do not benefit from reperfusion.

A concept similar to the MRA-DWI mismatch using CT data has been proposed by others. In the CT model, vessel occlusion determined by CT angiography (CTA) coupled with a qualitative assessment of collateral flow on CTA serves as a marker of brain tissue that is hypoperfused. The area of early parenchymal contrast enhancement on CTA source images may correspond with irreversibly damaged brain tissue. A comparison between CT and MRI data in source images may correspond with irreversibly damaged area of early parenchymal contrast enhancement on CTA serves as a marker of brain tissue that is hypoperfused. The use of CT perfusion imaging to identify the ischemic core and penumbra based on cerebral blood flow and cerebral blood volume characteristics. Other untested but potentially effective methods to select patients who are likely to benefit from reperfusion in the 3- to 6-hour time window include a mismatch based on transcranial Doppler and DWI data and mismatch based on transcranial Doppler and CT data.

The primary MRA-DWI mismatch criteria in our study included a DWI lesion volume <25 mL for patients with an occlusion of the first branch of the middle cerebral artery. This DWI threshold was based on previously published criteria for a clinical–diffusion mismatch. A smaller DWI lesion volume cutoff of 15 mL was prespecified for patients with reduced flow rather than occlusion of the first branch of the middle cerebral artery and patients with abnormal findings in smaller vessels (anterior cerebral artery and posterior cerebral artery) or more distal branches (second branch of the middle cerebral artery) because these patients are likely to have smaller PWI lesion volumes and therefore would require smaller DWI lesion volumes to qualify as a mismatch. Patients with an MRA-DWI mismatch according to the primary criteria were likely to have a favorable response associated with reperfusion, whereas patients who did not have an MRA-DWI mismatch tended to have less favorable outcomes when reperfusion occurred. Six alternative MRA-DWI mismatch criteria were explored to assess their ability to identify patients who have a favorable clinical response after early reperfusion. Of these, the strongest association between reperfusion and favorable clinical response was observed when MRA-DWI mismatch was defined more stringently as a DWI lesion <15 mL for MRA lesions rated either partial or complete occlusion (2 or 3). A potential benefit of this more stringent definition is a greater OR for favorable clinical response (OR, 26.0 versus 12.3), but a drawback is that fewer patients fulfill the stricter mismatch criteria.

The MRA-DWI mismatch model is a novel approach to select patients who are likely to benefit from reperfusion in the 3- to 6-hour time window after symptom onset. The relative ease of assessing MRA-DWI mismatch in the acute setting is a potential advantage over the PWI-DWI mismatch model. The criteria established for the MRA-DWI mismatch model in this study require validation in an independent cohort. Once validated, a randomized study of intravenous tPA administered in the 3- to 6-hour time window in patients selected based on their MRA-DWI mismatch pattern is required to demonstrate the clinical usefulness of the MRA-DWI mismatch pattern.

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