Magnetic resonance imaging (MRI) protocols for guiding stroke treatment involve the concept of a mismatch between the lesion volume on 2 sequences: diffusion-weighted imaging (DWI) and perfusion MR (PMR). When we look at the 2 sequences, in many cases we see that the diffusion deficit at an early time point is smaller than the perfusion deficit, demonstrating that there is more brain tissue at risk than is already infarcted. The difference in size between lesions captured by these 2 sequences may represent an area, that is related to the ischemic penumbra, the region of incomplete ischemia that lies next to the core of the infarction. It is not exactly the penumbra as measured by positron emission tomography (PET), but for our clinical routine it is close enough to give us an impression of tissue at risk. However, this is a snapshot and true only for a single time point: one hour later it may look very different. So even with this technology, you have to act quickly, otherwise the precondition is no longer present. We get this information together with magnetic resonance angiography (MRA) and we also rule out parenchymal hemorrhage with T2* imaging. When we and other groups started doing this, scanning took about 20 min, but now the time has been reduced to 10–11 min. That time does not include positioning the patient, and as anyone who has been in an MRI scanner without a stroke knows, it is not easy to stay still for 10 min, and 20–30% of stroke patients cannot tolerate this procedure.

There is hope that similar information can be obtained by computed tomography (CT). Since 2004, data have emerged indicating that with special algorithms in CT it is possible to show both the perfusion map and a map of different levels of perfusion abnormality, some of which, like the diffusion area, are so deep that they are incompatible with tissue survival. It is a completely different technique. Many people believe that it would be more widespread usable, since perfusion CT (PCT) and CT angiography (CTA) are available in more centers. That may be true, but clinical trial data are needed to confirm it.

**Open trials and case series**

We have evidence for use of the DWI/PMR (perfusion image, PI) mismatch from open studies, such as those by Tomalla et al and Köhrmann et al. A study that was recently submitted for publication has come from the German network comprising centers in Hamburg, Heidelberg, and Cologne. We pooled data from a total of 148 patients with MRI mismatch. Outcome evaluated using the modified Rankin scale was good for treatment with recombinant tissue plasminogen activator
(rt-PA) and the mortality rate was lower (Fig. 1). We found the same results in our single center study of 400 patients treated with rt-PA in Heidelberg over 7 years. Patients eligible for thrombolysis within 3 h were selected by CT or MRI and beyond 3 h only by MRI. There was no difference between the 3 groups in age or median National Institutes of Health Stroke Scale (NIHSS) score. The mortality rates were similar in the 3 groups, the lowest found among those patients treated after 3 h MRI-based. Modified Rankin scale scores were not statistically significantly different. In the late time window, there were fewer hemorrhages. So it is reassuring that we have a significant effect on avoidance of hemorrhages when we use MRI as an inclusion criterion.

A new trial called the “Take 5” project, involving our department at Heidelberg and colleagues in Erlangen, Cologne, Frankfurt, Hamburg, and Barcelona, looked at safety and efficacy endpoints in a total of 1,200 patients treated with rt-PA. We had 714 patients with CT-based treatment within 3 h, 322 with MRI-based treatment within 3 h, and almost 200 with MRI-based treatment beyond 3 h. It was not surprising that the results were similar to previous studies. Symptomatic intracranial hemorrhages (sICH) were not higher with MRI-based inclusion after 3 h, mortality (12.1%) was good, as would be expected in patients with NIHSS score of 12–13, and favorable clinical outcome in >40% (Table 1).

From these trials we do not see any indication that MRI-based selection after 3 h would yield worse results or be less safe. Overall it all appears to be more beneficial, although not always statistically significantly so, and feasible.

Among the other trials that have demonstrated the use of DWI/PMR mismatch is the Diffusion-Weighted Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) trial. The DEFUSE investigators did not use MRI as an inclusion criterion; they selected patients for rt-PA and then they did MRI. Patients were treated with rt-PA independently of what the MRI showed. Two types of mismatch patterns were identified: target mismatch and malignant mismatch. The malignant mismatch pattern is due to the size of the diffusion abnormality. This is already a large infarct, with a huge diffusion abnormality, almost a full-scale middle cerebral artery (MCA) infarct, so it is not surprising that thrombolysis in a case like that, where there is not much tissue to save, does not produce good results. In patients with the target mismatch and early recanalization, results were good, with 67% of this group having a favorable response to early reperfusion following rt-PA ad-
Table 1  Summary of results of "Take 5-project"

<table>
<thead>
<tr>
<th>Safety (all p = NS)</th>
<th>sICH</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT &lt; 3h</td>
<td>5.3%</td>
<td>13.7%</td>
</tr>
<tr>
<td>MRI &lt; 3h</td>
<td>3.1%</td>
<td>12.4%</td>
</tr>
<tr>
<td>MRI &gt; 3h</td>
<td>4.0%</td>
<td>12.1%</td>
</tr>
</tbody>
</table>

Efficacy univariate (all p = NS):
- Favorable Outcome: 35.6%, 38.8%, 42%
- Independent Outcome: 49.6%, 52.2%, 49.4%
- Responder: 32.4%, 35.7%, 34.5%

Efficacy multivariate:
Age and NIHSS highly significant predictors for all efficacy outcomes

Primary Endpoint: Favorable Outcome
- Use of MRI instead of CT: OR = 1.349 (CI 1.041–1.747, p = 0.023)
- For MRI < 3h: OR = 1.247
- For MRI > 3h: OR = 1.558

Conclusion:
- Largest study comparing MRI and CT based thrombolysis
- Significantly longer time windows and higher baseline NIHSS scores
- MRI based thrombolysis is at least as safe as, and possibly more effective than standard CT based thrombolysis.

ministration. In the patients with malignant mismatch [PI (>8 sec delay) >100 cc and/or DWI > 100cc], however, results were not very good, even with recanalization.

Randomized trials

There have been 2 Phase II randomized trials using rtPA with a 3–9 h time window: the Desmoteplase In Acute ischemic Stroke (DIAS) trial¹⁰ and the Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS) trial¹¹. A pooled analysis of these 2 trials is in press with Stroke. The DIAS trial was carried out in Germany, Singapore, and Australia, and the DEDAS trial was carried out in the United States and Germany. They were parallel, multicenter placebo-controlled, double-blind studies in patients age ≤ 85 years, with NIHSS score 4–20, who showed DWI/PI mismatch >20% on MRI within 8 h of their strokes. Treatment was begun within 3 to 9 h after stroke onset. Exclusion criteria were standard. DIAS enrolled 72 patients and DEDAS 37 patients and, respectively, they used 3 and 2 dosages of desmoteplase. Here I report the pooled intention to treat (ITT) analysis results only of those patients who received desmoteplase at doses of 90 μg/kg and 125 μg/kg. There were no major differences between the groups in typical demographic parameters such as age, time from onset of stroke, the 90 μg/kg, and baseline NIHSS score (11–12). The primary safety endpoint was the rate of sICH, and the primary efficacy co-endpoints were MRI reperfusion 4–8 h after treatment, a surrogate endpoint, and a clinical endpoint, good clinical outcome at 90 days.

These were very safe studies with low mortality rates. This was obviously a chance finding, as it is expected that in larger trials mortality rates will increase. However, it is still reassuring. Serious adverse events did not differ between the trials, and there was only one sICH in the whole pooled
Fig. 2 Pooled analysis of DIAS and DEDAS (ITT). MR reperfusion rates at 4–8 h and clinical outcome at day 90

Desmoteplase shows a significant shift for 125μg/kg as measured by the mRS at 90 days

Fig. 3 Comparison of outcome (modified Rankin Scale scores) between placebo and desmoteplase groups (Pooled analysis of DIAS and DEDAS)

analysis, in a patient on the 90 μg/kg dose of desmoteplase. Like the mortality result, this was also a chance finding and we do not expect to see that rate in a larger scale trial.

In the pooled analysis of the efficacy endpoints, the 62.5 μg/kg dose of desmoteplase did not appear to be effective. For the 90 μg/kg dose, the difference to placebo for both reperfusion and clinical outcome at day 90 was not statistically significant. For the 125 μg/kg doses, there was a highly significant superiority against placebo and there was a very high correlation between reperfusion rate and clinical outcome at 90 days that was very reassuring. This was shown by ITT as well as per protocol analyses (Fig. 2).

In this pooled analysis of the first 2 prospective randomized trials using diffusion/perfusion MRI both the mortality rate and the sICH rate appeared very low and both reperfusion rate and clinical
outcome were significantly improved with desmoteplase 125 µg/kg. Despite the small study size, disability is significantly reduced with 125 µg/kg. There were some problems with MRI inclusion in the DEDAS trial pooling at the 90 µg/kg and therefore the result for the 90 µg/kg dose was not as good as it might have been: 125 µg/kg appeared safe and effective (Fig. 3).

We are awaiting the results of the Phase IIb/III randomized trial, DIAS-2 (Desmoteplase In Acute Ischemic Stroke 2), a prospective randomized trial with the same study objective as the first DIAS trial. DIAS-2 allows inclusion of patients on the basis of perfusion CT, so this trial will not only tell us whether we can repeat DIAS and DEDAS in a second trial, but also whether CT is equivalent in its ability to select those patients. DIAS-2 is a 186-patient trial and recruitment and follow-up have been completed. We will present the results of the DIAS-2 trial on June at the European Stroke Conference in Glasgow, Scotland. I do not yet know the results, which I will see first the day before the conference starts, and I am looking forward to seeing them with great anticipation.

References