Imaging-based patient selection for Intra-arterial stroke therapy

Yoo, A.J.

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Chapter 2

Imaging-based Treatment Selection for Intravenous and Intra-arterial Stroke Therapies

Albert J. Yoo, Benjamin Pulli, R. Gilberto González

Abstract

Reperfusion therapy is the only approved treatment for acute ischemic stroke. The current approach to patient selection is based primarily on the time from stroke symptom onset. However, this algorithm sharply restricts the eligible patient population, and neglects large variations in collateral circulation that ultimately determine the therapeutic time window in individual patients. Time alone is unlikely to remain the dominant parameter. Alternative approaches to patient selection involve advanced neuroimaging methods including MRI diffusion-weighted imaging, MR and CT perfusion imaging and non-invasive angiography that provide potentially valuable information regarding the state of the brain parenchyma and the neurovasculature. There is now significant experience with these techniques, and there is emerging evidence on how specific imaging data may result in improved clinical outcomes. This article will review the major studies that have investigated the role of imaging in patient selection for both intravenous and intra-arterial therapies.
Introduction

Acute ischemic stroke (AIS) is the third leading cause of death and the leading cause of severe disability in adults. There are 795,000 strokes annually in the U.S., of which 692,000 (87%) are ischemic.¹ Current treatment approaches include intravenous tissue plasminogen activator (IV tPA), thrombolytic and/or mechanical intra-arterial therapies (IAT), and combined IV/IA bridging therapy.

There has been over a decade of research into the utility of neuroimaging for the evaluation of acute ischemic stroke. However, the issue of whether advanced imaging can lead to improved clinical outcomes remains open to debate. As a result, stroke duration continues to be the primary determinant of whether to treat.

Despite the lack of clear benefit, there remains a general optimism that advanced imaging can depict an individual patient’s specific cerebrovascular physiology, and that this information can be used to guide treatment decisions, particularly outside of the current, restrictive time windows.² The present article will address the current treatment selection paradigm and its limitations; review advanced CT and MRI stroke imaging techniques; and discuss the evidence-to-date evaluating the role of advanced imaging in patient selection for extended-window reperfusion therapies. This review will focus on MRI-based selection because the higher quality evidence concerns this technique. Where appropriate, we will discuss the analogous CT perfusion approaches.

Current approaches to patient selection: “Time is brain” and its limitations

Both IV and IA treatments are restricted by the time from stroke onset (Table 2.1). For IV tPA, the currently approved window is 3 hours based on the NINDS tPA Stroke Study.³ Results from the recent ECASS-3 trial⁴ have led to an American Heart Association guideline recommending IV tPA treatment between 3-4.5 hours in selected patients (Class I, LOE B).⁵ For IAT, the time window is 6 hours for thrombolysis and up to 8 hours for mechanical therapies.⁶⁷ This time-based approach has been demonstrated to be effective and safe by numerous randomized controlled trials (RCTs) and prospective registries,⁴⁹¹⁰ and has helped thousands of patients.¹¹ In this paradigm, a noncontrast head CT scan is performed to exclude intracranial hemorrhage (ICH) or extensive infarction (e.g., “greater than one-third of the middle cerebral artery [MCA] territory”).

The strict adherence to time windows reflects the idea that “time is brain”,¹² and is supported by pooled analyses of multiple randomized controlled trials (RCT) of IV
tPA,\textsuperscript{13-15} which have demonstrated that the odds for a good outcome decrease with increasing onset-to-treatment times (OTT). In a recent analysis,\textsuperscript{15} data from 3670 patients demonstrated that the adjusted odds of good 3-month outcome (defined as a modified Rankin Score \[mRS\] of 0-1) for IV tPA vs. placebo were 2.55 (95\%CI: 1.44-4.52) for 0-90 minutes, 1.64 (1.12-2.40) for 91-180 minutes, 1.34 (1.06-1.68) for 181-270 minutes and 1.22 (0.92-1.61) for 271-360 minutes \( (P=0.03) \).

Despite these findings, this time-based approach has been challenged in recent years for two main reasons. First, the time window for IV tPA is restrictive. Several investigations have shown that only 1-7\% of eligible patients receive IV tPA within the 3-hour window,\textsuperscript{16-18} mainly due to late presentation. Second, “time is brain” paints an incomplete picture of cerebrovascular physiology.\textsuperscript{19-20} While a time window may be effective on a population level, it may not hold for individual patients. From clinical experience, we know that there are patients who have large infarcts despite early presentation, and patients with negligible infarcts at later time points (Figure 2.1). Moreover, studies have demonstrated that there can be substantial volumes of viable penumbral tissue between 12-24 hours from onset.\textsuperscript{21-23}

![Patient 1: 66 year old female (A-C) with left MCA M1 occlusion (arrow) demonstrated on axial MIP (A) and small infarct (14 mL volume) on DWI (B) and ADC map (C). MR imaging was performed 8 hours, 58 min post ictus. Three-month mRS was 2. 52 year old male (D-F) with left MCA M1 occlusion (arrow) demonstrated on axial MIP (D) and extensive infarct (146 mL volume) on DWI (E) and ADC map (F). MR imaging was performed 4 hours, 16 min post ictus. Three-month mRS was 6.](image-url)
Not surprisingly then, recent data exploring the effect of time to reperfusion on outcome in IAT-treated patients is conflicting. In a pooled analysis of the IMS I and II trials, only time to angiographic reperfusion and age independently predicted good 3–month outcome (mRS 0-2) in 54 patients with terminal internal carotid artery (ICA) or proximal MCA occlusions who underwent successful reperfusion. On the other hand, in a pooled analysis of the MERCI and Multi-MERCI trials, neither time to procedure nor time to reperfusion was associated with good outcome (mRS 0-2) in 163 patients with anterior circulation proximal artery occlusion (PAO) who were successfully reperfused. These divergent results highlight the central problem with a time-based approach – it neglects the variable degree of cerebral blood flow (CBF) impairment.

In a landmark study, Jones et al. demonstrated using a primate model that both duration and degree of ischemia determined neuronal progression to cell death. With blood flow reduction below a certain threshold, clinical symptoms were observed but the tissue remained viable for several hours. At lower CBF thresholds, infarction ensued more rapidly. These findings have been confirmed in humans using positron emission tomography (PET).

For anterior circulation strokes, the pial collateral circulation to the MCA territory, primarily from the anterior cerebral artery, is the main determinant of CBF impairment, and thus the rate of neuronal loss. The strength of the collateral circulation is variable between patients, and has been shown to be a significant predictor of clinical outcome and tissue fate. Therefore, a more accurate statement would be “time and collaterals are brain”. This idea is further supported by studies of extended window therapies, which have demonstrated two relevant points: 1) there may be a clinical benefit to physiology-based patient selection using advanced imaging beyond 3 hours; and 2) in patients selected based on a favorable physiology, onset-to-treatment time is not a predictor of outcome.

Imaging the acutely ischemic brain

Considerable evidence demonstrates that final infarct size is a critical determinant of clinical outcome. In a substudy of the ASAP trial involving 169 patients with median NIH stroke scale (NIHSS) score of 6 (mild-moderate severity), infarct growth (at post-stroke day 5) was an independent predictor of excellent 90-day outcome (mRS 0-1; P=0.01). The adjusted odds ratio for an excellent mRS score was reduced with an increase in infarct volume (OR 0.57 [95%CI: 0.37-0.88] for every 10-mlL increase). In a subgroup analysis of the EPITHET trial which included 72 patients with median NIHSS score of 12 (moderate-severe strokes), infarct volume (on post-stroke day 3-5) had a strong correlation with 90-day NIHSS score (Spearman rho=0.81; P<0.01). Finally, in a
study of 81 IAT patients with anterior circulation PAO and median NIHSS score of 18, the final infarct volume was the best discriminator of good 3-month outcome (mRS≤2) in ROC analysis (AUC=0.883).

Reperfusion therapy limits the size of the final infarct by salvaging the ischemic penumbra. Patients with large baseline infarcts have little to no hope of treatment benefit, and should be excluded from the risks of therapy, which include iatrogenic emboli, intracerebral hemorrhage (ICH) and reperfusion edema. Therefore, imaging of parenchymal injury at the time of presentation can provide important information for treatment decision making.

Noncontrast CT

As mentioned previously, the major RCTs that guide current clinical practice employed noncontrast CT (NCCT) for assessment of parenchymal injury. Patients were excluded from therapy if they had infarcts that involved greater than one-third of the MCA territory or that resulted in severe edema or mass effect (Table 2.1).

Table 2.1 Clinical trials evaluating the time is brain paradigm (NCCT based imaging).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type</th>
<th>N</th>
<th>Time [min]</th>
<th>Primary Outcome (PO)</th>
<th>PO reached</th>
<th>SICH</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS part 1</td>
<td>RCT</td>
<td>291</td>
<td>0-180</td>
<td>24 h NIHSSS</td>
<td>No</td>
<td></td>
<td>6.4 vs. 0.6%</td>
</tr>
<tr>
<td>NINDS part 2</td>
<td>RCT</td>
<td>333</td>
<td>0-180</td>
<td>90 d mRS</td>
<td>Yes</td>
<td></td>
<td>FDA approval for &lt;3 hours</td>
</tr>
<tr>
<td>ATLANTIS part A</td>
<td>RCT</td>
<td>142</td>
<td>0-360</td>
<td>30 d NIHSSS</td>
<td>No</td>
<td>11 vs. 0%</td>
<td></td>
</tr>
<tr>
<td>ATLANTIS part B</td>
<td>RCT</td>
<td>547</td>
<td>180-300</td>
<td>90 d NIHSSS</td>
<td>No</td>
<td>7 vs. 1.1%</td>
<td></td>
</tr>
<tr>
<td>ECASS</td>
<td>RCT</td>
<td>620</td>
<td>0-360</td>
<td>90 d mRS</td>
<td>No</td>
<td></td>
<td>19.8 vs. 6.5%</td>
</tr>
<tr>
<td>ECASS-II</td>
<td>RCT</td>
<td>800</td>
<td>0-360</td>
<td>90 d mRS</td>
<td>No</td>
<td></td>
<td>8.8 vs. 3.4%</td>
</tr>
<tr>
<td>ECASS-III</td>
<td>RCT</td>
<td>821</td>
<td>180-270</td>
<td>90 d mRS</td>
<td>Yes</td>
<td>2.4 vs.0.2%</td>
<td></td>
</tr>
<tr>
<td>SITS-MOST [1]</td>
<td>RCT</td>
<td>6483</td>
<td>664 vs. 11865</td>
<td>0-180</td>
<td>5IH, mortality</td>
<td>Yes [3]</td>
<td>7.3 vs. 8.3%</td>
</tr>
<tr>
<td>SITS-ISTR [2]</td>
<td>RCT</td>
<td>664</td>
<td>180-270</td>
<td>90 d mRS</td>
<td>Yes [7]</td>
<td>2.2 vs. 1.6%</td>
<td></td>
</tr>
</tbody>
</table>

1Prospective, open, observational patient registry. 2Significant at the P<0.05 level. 3difference to pooled data from RCTs was not significant. 4P=0.24. 5664 patients between 3 and 4.5 hours were compared to 11865 patients between 0 and 3 hours from symptoms onset. 6Rate of parenchymal hematoma. 7No significant difference between two groups (P=0.42). 8Symptomatic ICH unless otherwise indicated.
Using NCCT for parenchymal assessment is problematic for two reasons. First, it suffers from a high degree of inter-rater variability for detecting early ischemic changes, \(^{50-52}\) which include parenchymal hypoattenuation, loss of gray-white matter distinction, and cortical swelling. \(^{52}\) Second, NCCT demonstrates poor sensitivity (20%-75%) for detecting acute infarction within the 6- to 8-hour window. \(^{51-56}\) One study reported a sensitivity of 14%-43% for identifying infarcts larger than one-third of the MCA territory within seven hours of stroke onset (Figure 2.2). \(^{55}\) Hence, the current imaging criterion is highly permissive, and excludes only the largest and most well-established infarcts from reperfusion therapy. \(^{57}\) For practical purposes, treatment selection is determined primarily by the time window.

Figure 2.2  NCCT (A) of a 45 years old male demonstrates subtle hypodensity in putamen and possible effacement of sulci at the frontal operculum. DWI (B) and ADC map (C) on a similar level show extensive acute ischemic infarct involving basal ganglia, insula and cortical regions of the frontal and temporal lobe. On a different slice, NCCT (D) with subtle hypodensity in the deep white matter, otherwise inconspicuous. DWI (E) and ADC map (F) show extensive infarction of white and grey matter in the frontal and temporal lobes. Time between CT and MRI was 45 minutes.
In order to improve NCCT evaluation of hyperacute ischemic stroke, a more rigorous approach to image analysis is necessary. In current practice, early NCCT changes are poorly defined and may signify varying degrees of ischemia and viability.\textsuperscript{52,58-59} For example, two recent studies have shown that isolated cortical swelling may indicate penumbral tissue while hypoattenuation appears to represent infarct core.\textsuperscript{58-59} Further work needs to be carried out, particularly with automated Hounsfield unit analysis.

**Advanced imaging of the infarct core**

Of the available MRI and CT measurements, abnormalities detected on DWI are considered the most reliable estimate of the infarct core. The loss of cellular energy metabolism causes a failure of membrane ionic pumps resulting in cytotoxic edema and restricted diffusion of water, which is detectable using diffusion-weighted imaging. DWI is highly sensitive (91-100\%) and specific (86-100\%) in the identification of early ischemic brain injury (<6 hours from onset),\textsuperscript{53,60-61} and has similar accuracy for the prediction of cortical infarction as \textsuperscript{11}C flumazenil PET,\textsuperscript{62} a reliable marker of neuronal integrity.

However, certain findings have led some to question the value of DWI for assessing the infarct core.\textsuperscript{63} First, the pathophysiologic processes within the DWI lesion are heterogeneous, as evidenced by a high spatial variability in the metabolic rate of oxygen, oxygen extraction fraction, and cerebral perfusion within individual lesions.\textsuperscript{64-65} Moreover, animal studies demonstrate that the DWI lesion is more closely correlated to areas of pH alteration due to anaerobic metabolism,\textsuperscript{66} suggesting that in the hyperacute phase DWI may depict still viable tissue. Most importantly, there have been several reports of DWI lesion reversibility after treatment, with reported rates ranging from 8\%-44\%.\textsuperscript{67-71}

However, the clinical significance of DWI lesion reversal remains unclear. To date, it has not been demonstrated to improve clinical outcomes.\textsuperscript{69,72} Tissue reperfusion appears to be a prerequisite for this phenomenon.\textsuperscript{67,70} Other predictors include earlier time to imaging\textsuperscript{68,70} and smaller reductions in the apparent diffusion coefficient,\textsuperscript{70} likely reflecting milder reductions in blood flow.\textsuperscript{73} Importantly, the mean volume of tissue reversal is relatively small (5.1 cm\textsuperscript{3} -16 cm\textsuperscript{3}).\textsuperscript{52,67,69-70} While such small volumes may translate to clinical improvement, it is more likely that any benefit associated with DWI reversal is related to accompanying tissue reperfusion and penumbral salvage. Moreover, delayed re-growth into a previously observed diffusion abnormality frequently occurs,\textsuperscript{67-68} even when blood flow is restored.\textsuperscript{74-75} Finally, the true frequency of DWI reversal may be lower than previously reported when chronic infarct involution is taken into consideration. In a post hoc analysis of the EPITHET trial,\textsuperscript{76} true DWI reversal was seen in only 6.4\% of patients with a negligible median reversal volume of 2.7 ml (IQR: 1.6-6.2 ml).
Taken together, the evidence indicates that DWI is currently the most accurate and well validated method for assessing acute infarction in the treatment setting, an opinion supported by multiple expert panels (Class I, level of evidence A). Advanced CT methods for delineating the infarct core include parenchymal hypoa attenuation on CT angiographic source images (CTA-SI) and depressed cerebral blood volume (CBV) on processed CT perfusion (CTP) maps. However, these methods are less validated (Class IIb, level of evidence B), and require further study. For example, it has been demonstrated recently that CBV values are dependent on the duration of PWI scanning, and that the majority of DWI-positive regions may have elevated CBV.

Advanced imaging of hypoperfused (penumbral) brain tissue

$H_2^{15}$O PET and diffusible-tracer techniques such as 99mTc-HMPAO SPECT (single-photon emission CT) are considered the reference standards for quantifying cerebral perfusion, but they are not practical in the clinical setting. MR and CT perfusion imaging, on the other hand, are widely available and have been studied extensively in AIS. They are dynamic contrast methods, whereby post-processing of the source imaging data produces a series of maps that describe the cerebral hemodynamics. Importantly, post-processing can be performed in several different ways, and may yield different results even for the same patient. Indirect parameters, such as bolus arrival time and time-to-peak (TTP), are easy to calculate, but are thought to be less accurate than parameters derived from deconvolution with an arterial input function (AIF). Deconvolution corrects for bolus delay and dispersion up to the level of the AIF, and produces maps of tissue-level perfusion parameters such as CBV, cerebral blood flow (CBF) and mean transit time (MTT).

A major limitation of MR and CT perfusion imaging is that they are not reliable for absolute quantification of cerebral perfusion. Numerous studies have demonstrated poor reproducibility and significant variability in these techniques. Given these limitations, a semiquantitative approach has been advocated in which a simple volumetric mismatch between the infarct core and the larger region of hypoperfusion constitutes an “operational ischemic penumbra”. The most widely studied method is the MRI diffusion-perfusion mismatch.

Commonly used parameters in MR perfusion weighted imaging (PWI) are TTP, MTT and Tmax, the latter two requiring deconvolution-based processing. TTP is defined as the time to maximum signal intensity loss during contrast transit, and is dependent on multiple factors, including MTT, bolus arrival time and CBF. MTT is the average time for the contrast molecule to traverse the voxel, and has been used in several trials including DIAS, DEPAS, and DIAS-2. It has been quoted as having the most direct physiologic correlation with tissue survival because oxygen extraction is diffusion-limited in brain capillaries and therefore determined by vascular transit time.
Chapter 2

is the time at which the tissue residue function reaches its maximum, or when the injected contrast arrives in a particular brain voxel. Tmax is abnormal in collaterally perfused tissue even if CBF is normal. Therefore, it does not describe the hemodynamic status of the tissue itself. Several studies have used Tmax as the PWI method of choice, such as DEFUSE and EPITHET.

Imaging the cerebral vasculature

The initial event in ischemic stroke is vascular occlusion. Angiographically-controlled studies have demonstrated that identification of the occluded vessel provides additional prognostic information beyond clinical variables alone. Specifically, the presence of a proximal arterial occlusion (e.g., ICA, proximal MCA or basilar artery) is associated with worse clinical outcomes. In a study of 480 patients, patients with PAO or significant parenchymal involvement consistent with PAO accounted for all the deaths, had longer hospital stays, and were more likely to be discharged to a rehabilitation facility (all outcomes, P<0.0001).

According to recent guidelines, noninvasive vessel imaging should be performed whenever possible in patients with suspected stroke or transient ischemic attack. CT angiography is the best noninvasive test for identifying major intracranial vessel occlusion. In one study of 44 consecutive patients who underwent CTA followed by IAT, CTA demonstrated 98.4% sensitivity, 98.1% specificity and 98.2% accuracy for large vessel occlusions when compared to the gold standard digital subtraction angiography (DSA). Furthermore, CTA has a high interobserver reliability. Identification of PAO, particularly in the second-order M2 (MCA) and A2 (ACA) branches, is facilitated by “collapsed” maximum intensity projection images, which can be constructed immediately at the CT scanner console and along three orthogonal planes (Figure 2.3). MR angiography (MRA) is another widely used noninvasive test, and is performed with 3D time-of-flight technique (3D TOF) or after gadolinium administration. Compared to CTA, it is more sensitive to patient motion artifact, as well as to flow artifact. The latter may result in overestimation of vessel stenosis. However, for the question of PAO, 3D TOF MRA performs reasonably well, with a sensitivity of 84%-87% and a specificity of 85%-98% compared to DSA. The interobserver agreement is fair to moderate (kappa=0.5).
Imaging selection for intravenous thrombolysis

Evidence supporting the mismatch hypothesis

Until the ECASS-3 results, previous studies that employed NCCT-based selection failed to extend the time window for IV tPA beyond 3 hours. ATLANTIS, ECASS, and ECASS-2 could not demonstrate a clinical benefit that outweighed treatment risk in the 5- to 6-hour window. In comparison, multiple studies employing MRI diffusion-perfusion mismatch have demonstrated positive clinical results for extended window treatment with IV tPA, and provide the strongest evidence for this imaging approach (Table 2.2).

In large multicenter studies, patient selection using the perfusion-diffusion mismatch was demonstrated to safely and effectively extend the treatment window for IV tPA up to six hours. The most frequently employed mismatch definition was a perfusion lesion at least 20% larger than the diffusion lesion. Furthermore, patients were excluded if they had extensive infarcts greater than one-third or one-half of the MCA territory. Notably, patients with a PWI/DWI mismatch treated with IV tPA beyond 3 hours appeared to do just as well as patients treated within the 3-hour window using traditional NCCT criteria. In a multi-center retrospective study of 1210 patients, there were no significant differences in favorable 3-month clinical outcome (mRS 0-1; 35.4% vs. 40.0%), symptomatic ICH (sICH; 5.3% vs. 4.4%) and mortality (13.7% vs. 13.3%) between patients treated within 3 hours using NCCT versus those treated beyond 3 hours based on a 20% PWI/DWI mismatch. In multiple logistic regression, use of MRI beyond 3 hours significantly increased the odds for a favorable outcome.
compared to CT-based treatment within 3 hours (OR: 1.467; 95% CI: 1.017 to 2.117). The odds of sICH were reduced to approximately half (OR: 0.520, 95% CI: 0.270 to 0.999, P<0.05) with MRI-based selection. Importantly, OTT was not a predictor of safety or efficacy in univariate or multivariate analysis. The perfusion imaging techniques were heterogeneous among the centers and included non-thresholded MTT and TTP with (>4 seconds delay) and without thresholding. Other studies have found similar results (Table 2.2),38,115-116 supporting the idea that a favorable cerebrovascular physiology may be more important than ischemic duration for extended window therapy.

Table 2.2 Clinical trials supporting the mismatch hypothesis (MR-based imaging).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type</th>
<th>N</th>
<th>Time (min)</th>
<th>Primary Outcome (PO)</th>
<th>PO reached</th>
<th>SICH</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFUSE</td>
<td>RCT</td>
<td>74</td>
<td>180-360</td>
<td>30 d NIHSSS</td>
<td>Yes</td>
<td>9.5%</td>
<td>First evidence for mismatch hypothesis (5)</td>
</tr>
<tr>
<td>DIAS-I</td>
<td>RCT</td>
<td>104</td>
<td>180-540</td>
<td>90 d mRS, Reperfusion</td>
<td>Yes</td>
<td>2.2%</td>
<td>2.2 vs. 0% Reperfusion is associated with favorable outcome in patients with MRI mismatch</td>
</tr>
<tr>
<td>DEDAS</td>
<td>RCT</td>
<td>37</td>
<td>180-540</td>
<td>90 d mRS, Reperfusion</td>
<td>Yes</td>
<td>None</td>
<td>Desmoteplase is safe to use within 3 – 9 hours.</td>
</tr>
<tr>
<td>Schelling et al.</td>
<td>RCT</td>
<td>1210</td>
<td>0-1032</td>
<td>90 d mRS (3)</td>
<td>Yes (6)</td>
<td>n.s.</td>
<td>MRI selection for thrombolysis is safer and more efficacious than NCCT selection</td>
</tr>
<tr>
<td>Köhrmann et al.</td>
<td>RCT</td>
<td>382</td>
<td>&gt;180</td>
<td>90 d mRS (3)</td>
<td>Yes (6)</td>
<td>3 vs. 9% (4) Patients with MRI mismatch can be treated up to 6 hours</td>
<td></td>
</tr>
<tr>
<td>Thomalla et al.</td>
<td>RCT</td>
<td>174</td>
<td>0-360</td>
<td>90 d mRS (7)</td>
<td>Yes (6)</td>
<td>3 vs. 8% (4)</td>
<td></td>
</tr>
</tbody>
</table>

RCT (randomized controlled trial); NIHSSS (NIH Stroke Scale score); BI (Barthel index); mRS (modified Rankin Scale score); SICH (symptomatic intracranial hemorrhage); OTT (onset to treatment time). 1Study of intravenous desmoteplase. Patients were selected based on perfusion-diffusion mismatch. 2Reperfusion was assessed within 4-8 hours after IV tPA with MRI. 3For 125 μg/kg dose. 4One patient who received 90 μg/kg dose. 5Significant for clinical outcome but not for reperfusion at 125 μg/kg dose in target population. 6Prospective, open, observational study. Selection of patients for treatment was not based on MRI mismatch. 7Clinical outcome was compared between patients selected with NCCT, MRI (<3hrs) and MRI (>3hrs). 8Significant at the P<0.05 level. 9MRI based patient selection >3 hours led to similar or better clinical outcome than patient selection based on NCCT. 10Clinical outcome was compared between selection with NCCT (<3hrs) and MRI (3-6hrs).

Trials of intravenous desmoteplase

Direct RCT evidence supporting the utility of mismatch-based selection was provided by trials of desmoteplase, a thrombolytic agent with high fibrin specificity, low neurotoxicity and a long half-life.117-118

In the randomized, placebo-controlled phase II DIAS trial,39 patients with OTT within 3-9 hours, a perfusion abnormality of 2 cm in diameter involving hemispheric gray matter and a perfusion-diffusion mismatch of ≥20% were included and randomized to
Magnetic resonance imaging (MRI)-based selection for intra-arterial stroke therapy

62.5 µg/kg, 90 µg/kg, 125 µg/kg, or placebo (Part 2, n=57 patients). Mismatch volumes were assessed by visual estimation. Compared with placebo (n=27), the 125 µg/kg desmoteplase dose (n=15) resulted in a higher reperfusion rate on MRI performed after 4 to 8 hours (71.4% vs. 19.2%, P=0.001) and higher rates of 90-day favorable clinical outcome (60% vs. 22.2%, P=0.009). As in other studies, OTT interval was not associated with reduced treatment effect. In a similar study design, DEDAS confirmed the clinical benefit of the 125 µg/kg desmoteplase dose relative to placebo in patients who fulfilled all MRI selection criteria, without a difference in sICH rate or mortality.

The clinical response of mismatch patients to reperfusion

The beneficial clinical response of mismatch patients to documented reperfusion was demonstrated in DEFUSE, a phase II study examining 74 consecutive patients treated with IV tPA between 3-6 hours after stroke onset. Importantly, treatment selection was based on NCCT, not on an MRI mismatch. A total of 1,020 patients were screened for 74 patients (7.2%). Patients with a baseline PWI/DWI mismatch (mismatch ratio ≥20%, and absolute mismatch ≥10 ml) who underwent early reperfusion (>30% reduction in PWI lesion volume on MRI performed 3-6 hours after IV tPA treatment) had better outcomes than mismatch patients without reperfusion (OR, 5.4; 95% CI, 1.1-25.8). Additionally, patients without a PWI/DWI mismatch did not appear to benefit from early reperfusion, although there were only 11 patients without a mismatch in the study. Penumbral imaging utilized Tmax with a 2-second delay.

CT perfusion-based mismatch (e.g., CBV-MTT mismatch) has been shown to provide similar assessments of treatment eligibility (e.g., infarct core <1/3 MCA territory and mismatch ≥20%) to the MRI-based approach. However, the lack of standardized post-processing and analysis, including the choice of perfusion parameter, and the absence of well-validated thresholds limit the utility of this approach at this time.

The limitations of the mismatch approach

Despite the favorable data in support of the mismatch hypothesis, there is no conclusive evidence that the mismatch alone identifies patients who will respond to thrombolysis (Table 2.3). This uncertainty was recently highlighted by the results of the phase III DIAS-2 study, which failed to confirm the DIAS and DEDAS findings. In this study, stroke patients with a 20% visual mismatch on either MRI or CT perfusion were randomized in a 1:1:1 fashion to 90 µg/kg IV desmoteplase, 125 µg/kg IV desmoteplase and placebo. Among the low-dose, high-dose and placebo groups respectively, the rates of favorable clinical outcome at 90 days were 47%, 36% and 46%; the rates of SICH were 3.5%, 4.5% and 0%; and the mortality rates were 11%, 21% and 6%. One-third of enrolled patients were evaluated with CT perfusion.
Table 2.3 Clinical trials against the mismatch hypothesis (MR and/or CT perfusion imaging).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type</th>
<th>N</th>
<th>Time (min)</th>
<th>Primary Outcome (PO)</th>
<th>PO</th>
<th>SICH</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPITHET</td>
<td>RCT</td>
<td>101</td>
<td>180-360</td>
<td>Infarct growth &lt;0.05</td>
<td>No</td>
<td>Yes</td>
<td>Failure to demonstrate difference in reperfusion, infarct growth or clinical outcome between mismatch and non-mismatch patients. For IV tPA and placebo.</td>
</tr>
<tr>
<td>DIAS-ii (6)</td>
<td>RCT</td>
<td>186</td>
<td>180-540</td>
<td>90 d combined NIHSSS/mRS/BI</td>
<td>No</td>
<td>4.1 vs. 0%</td>
<td>No clinical benefit demonstrated for mismatch patients treated with desmoteplase between 3 to 9 hours.</td>
</tr>
<tr>
<td>Mishra et al. (11)</td>
<td>RCT</td>
<td>502</td>
<td>0-540</td>
<td>90 d NIHSSS or mRS</td>
<td>No</td>
<td>NS</td>
<td>No clinical benefit with IV thrombolysis in mismatch patients beyond 3 and up to 9 hours.</td>
</tr>
</tbody>
</table>

RCT (randomized controlled trial); NIHSSS (NIH Stroke Scale score); BI (Barthel index); mRS (modified Rankin Scale score); SICH (symptomatic intracranial hemorrhage); NS (not significant). 1 Defined as a ratio of geometric means. Comparison is between patients with and without a mismatch treated with IV tPA. 2 Mismatch vs. placebo (significant at P<0.05 level). 3 Patients were not selected based on an imaging mismatch. 4 IV desmoteplase treatment: 90 and 125 μg/kg doses. 5 Patients were selected based on 20% imaging mismatch using MRI or CT perfusion. There was a significant increase in mortality with desmoteplase treatment. 6 Pooled analysis of DEFUSE, EPITHET, DIAS, DIAS II, and DEDAS. 7 IV thrombolysis was associated with increased reperfusion/recanalization but not with favorable clinical outcome. There was a nonsignificant increased odds of mortality and SICH with treatment, after excluding data from abandoned desmoteplase doses. 8 After excluding data from abandoned desmoteplase doses.

Additionally, the EPITHET trial, a phase II placebo-controlled, randomized trial of IV tPA administered 3 to 6 hours after stroke onset, failed to demonstrate any significant difference in the primary endpoint of infarct growth, or in reperfusion and clinical outcomes, between patients with a PWI/DWI mismatch (PWI-DWI volume >1.2, and absolute mismatch volume ≥10 ml) and those without a mismatch, for both the IV tPA and placebo groups. As in DEFUSE, MRI findings were not used for patient selection or treatment allocation. These results are consistent with previous studies which have demonstrated that the PWI/DWI mismatch does not predict infarct growth, and that lesion growth is equally common in patients with and without a mismatch.

A recent meta-analysis of the DEDAS, DIAS, DIAS II, DEFUSE and EPITHET trials analyzed the data from 502 mismatch patients who were treated with intravenous thrombolysis or placebo beyond 3 hours. While patients with an imaging mismatch demonstrated higher rates of reperfusion with thrombolysis (adjusted OR=3.0; 95% CI, 1.6-5.8), there was no significant improvement in favorable clinical outcome by thrombolytic therapy (a-OR=1.3; 95% CI, 0.8-2.0). Furthermore, there was a significant increase in mortality and SICH after treatment, but these endpoints did not remain significant after exclusion of abandoned desmoteplase doses. These negative results suggest that the clinical and
tissue response to reperfusion therapy may not be dependent strictly on the presence of a mismatch as it is currently defined.\textsuperscript{126}

Several fundamental problems with the mismatch approach exist and may help to explain the conflicting data. First, despite its widespread use, the 20% PWI/DWI mismatch remains an arbitrary value.\textsuperscript{88,122,127} Recent studies have sought to optimize this definition. A post-hoc analysis of 45 patients from the DEFUSE study found that a PWI/DWI ratio of 2.6 yielded the highest sensitivity (90%) and specificity (83%) for identifying a favorable clinical response to early reperfusion.\textsuperscript{128} Similarly, an unpublished analysis of the EPITHET dataset found that a PWI/DWI ratio of 2 was a better predictor of clinical outcomes than the 20% mismatch.\textsuperscript{129} Further studies are required to validate these findings.

Additionally, there is no consensus as to which perfusion parameter should be employed in defining the mismatch.\textsuperscript{122,130} TTP, Tmax and MTT are commonly used because lesions are easily discernible. However, the choice of parameter affects the perfusion lesion volume and hence the quantitative mismatch.\textsuperscript{88-89,127} It has been shown that selection using different parameters would result in 9 to 63% of patients receiving treatment, a range which is unacceptable for both clinical trials and practice.\textsuperscript{89}

Another issue is the use of visual estimation for assessing mismatch size. A study by Coutts et al.\textsuperscript{131} demonstrated that visual assessment suffers from a high degree of measurement error (standard error of the mean=21.6%). In the DEDAS study, visual assessment overestimated the true mismatch in 16% of cases.\textsuperscript{96}

The most significant problem with the mismatch approach is that the commonly used measures of abnormal perfusion (MTT and TTP) overestimate the true territory at risk.\textsuperscript{132,140} DEFUSE and EPITHET used a Tmax delay of 2 seconds, which was subsequently shown to encompass areas of benign oligemia.\textsuperscript{141} This poor specificity explains why patients with significant extra- or intracranial vascular stenosis have a larger PWI/DWI mismatch but less infarct growth than patients without stenosis.\textsuperscript{142-143} Therefore, the same degree of mismatch may have variable consequences in different patients.

One proposed method to improve tissue prediction using perfusion imaging is the use of threshold techniques.\textsuperscript{130,144} Despite the questionable reliability of perfusion measurement, several studies have sought to establish thresholds that distinguish critical hypoperfusion from benign oligemia.\textsuperscript{81,134-135,138,141,145-149} Importantly, this analysis must be restricted to patients with persistent occlusions, and only a fraction of studies excluded patients with documented reperfusion or dramatic clinical improvement.\textsuperscript{81,127,134-135,146} Unfortunately, these studies utilized different perfusion
parameters in their analysis, preventing confirmation of their results. The reported thresholds were an MTT delay of 4 to 6 seconds, a relative MTT of 145%, and a Tmax delay of 4 to 6 seconds and a first moment prolongation of 3.5 seconds, while one study found that no perfusion parameter distinguished benign oligemia from final infarction (cf. erratum). Other studies have compared MR perfusion with H\textsubscript{2}O PET-derived CBF and have found that a TTP delay between 4-6 seconds best identifies penumbral flow (e.g., CBF <20 ml/100 g/min). However, this threshold did not reliably correspond to penumbra as defined by PET oxygen extraction fraction >150%. Using MTT prolongation, thresholds of >5.3 seconds and 6 seconds were found to best identify CBF <20 ml/100 g/min. However, these findings disagreed with another study which found an optimal MTT threshold of >10 seconds that corresponded to xenon CT-derived CBF <20 ml/100 g/min.

Based on these results, the use of viability thresholds for clinical decision-making cannot be recommended until there is stronger evidence. In order to validate clinically useful perfusion thresholds, not only will it be important to decide on which perfusion parameters to measure, it will be necessary to use standardized perfusion processing methods and software, as these can introduce variability in perfusion measurement. Even if these issues are addressed, a critical limitation of perfusion imaging is that it measures blood flow at a single moment in time. This is likely insufficient as perfusion may vary over time due to changes in local perfusion pressure and recruitment or loss of collaterals.

**Alternative methods for penumbral selection**

Because a mismatch ratio is a relative measure, the same ratio can equate to different absolute tissue volumes and hence represent varying stroke severities. Despite identical imaging selection criteria for DIAS, DEDAS and DIAS-2, baseline strokes in DIAS-2 were less severe across all study groups (average NIHSS of 9 vs. 12 in DIAS and DEDAS). Similarly, DWI lesion volumes and absolute mismatch volumes were significantly smaller in DIAS-2, despite the higher relative mismatch volume, and the rate of vessel occlusion was lower. The less severe stroke population in DIAS-2 helps to explain the high placebo response rate that contributed to the failure of this study. Likewise, despite similar imaging criteria between DEFUSE and EPITHET (e.g., Tmax threshold of 2 seconds), the DEFUSE cohort had lower baseline NIHSS scores (11.5 vs. 13) and smaller baseline DWI (10 vs. 21 ml) and PWI (48 vs. 192 ml) lesion volumes.

To address the mismatch problem, approaches based on absolute lesion volume have been proposed. In support of this concept, a post hoc analysis of EPITHET recently demonstrated that DWI and PWI lesion volumes influence clinical response to IV tPA, while mismatch ratios do not. This finding is reasonable when one considers that a small territory at risk will likely result in a favorable clinical outcome even if the
perfusion abnormality is 20% larger than the core infarct defined by diffusion imaging. Similarly, a significant neurologic deficit owing to a large core infarct will not be influenced by improved perfusion in the surrounding tissue. It is the size and location of the infarct and the territory at risk that are critical to outcome.

One alternative based on volume considerations is the clinical-DWI mismatch (CDM). Dávalos et al. defined CDM as a baseline NIHSS score ≥8 and admission DWI lesion volume ≤25 ml. In their study, 87 of 166 (52%) hemispheric stroke patients presenting within 12 hours were found to have CDM. CDM patients were more likely to have early neurological deterioration (NIHSS score worsening ≥4 at 72 hours) than those with NIHSS <8 (OR 9.0; 95%CI 1.9-42) and those with DWI volume >25 ml (OR 2.0; 95%CI 0.8-4.9). Furthermore, CDM was associated with the greatest infarct growth at days 3 and 30 (P<0.001). The association of CDM with greater infarct growth was also reported by Prosser et al., who also found that CDM was highly specific (93%) but not sensitive (53%) for identifying a PWI/DWI mismatch >20%. However, other studies were not able to demonstrate that CDM was associated with an improved clinical response to IV-tPA or reperfusion. Similarly, an analogous NCCT-based approach failed to predict response to IV-tPA in the CLOTBUST dataset.

Another recently described approach utilizes DWI and PWI lesion volumes in conjunction with NIHSS thresholds. In a study of 54 AIS patients imaged using MRI within 9 hours of onset, baseline DWI and MTT volumes predicted independent outcome (mRS 0-2) at 3 months better than mismatch volume or percent mismatch. Thresholds identifying poor outcome (mRS 3-6) with 100% specificity were DWI lesion volume >72 ml and NIHSS score >20. Thresholds identifying good outcome with 100% specificity were MTT lesion volume <47 ml and NIHSS score <8. Using these combined thresholds, dichotomized outcome was predicted in 70% of cases, higher than for clinical (43%) or imaging (54%) thresholds alone (P=0.01). Using these criteria, a target population for treatment would be patients with DWI lesion volume ≤72 ml, MTT volume ≥47 ml and NIHSS score ≥8 and ≤20. However, this approach awaits clinical validation in an independent cohort.

A third approach combines vessel imaging and baseline DWI lesion volume. In a post hoc analysis of DEFUSE, the MRA-DWI mismatch was defined as (1) a proximal artery occlusion with DWI lesion volume <25 ml; or (2) proximal artery stenosis or abnormal distal vessel with DWI lesion volume <15 ml. Proximal arteries were the terminal ICA and MCA M1 segment. Distal arteries were the MCA M2 segments and the anterior and posterior cerebral arteries. Twenty-seven of 62 (44%) patients had an MRA-DWI mismatch. The agreement between the MRA-DWI and PWI-DWI mismatch models was 63% (95%CI, 50-74%). Early reperfusion (3-6 hours after tPA administration) was associated with increased odds of favorable outcome in patients with MRA-DWI.
mismatch (OR 12.3; 95% CI, 1.8-84.0). There was a decrease in favorable outcomes with early reperfusion among patients without MRA-DWI mismatch (OR 0.2; 95% CI, 0.0-0.8), although this was not significant after adjusting for baseline characteristics.

Ongoing imaging studies of IV thrombolysis

Despite numerous studies, there is conflicting evidence that perfusion imaging improves clinical outcomes.\textsuperscript{161} The mismatch approach, in particular, awaits further testing. Multiple ongoing trials are exploring MRI- and CT-based imaging signatures for identifying favorable candidates for intravenous reperfusion therapies. (Table 2.4)

### Table 2.4 Ongoing imaging trials of IV thrombolysis.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type</th>
<th>N</th>
<th>Time (min)</th>
<th>Imaging criteria</th>
<th>Drug</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIAS-IV</td>
<td>RCT</td>
<td>400</td>
<td>180-540</td>
<td>MRA/CTA\textsuperscript{4}</td>
<td>Desmoteplase</td>
<td>90 d mRS</td>
</tr>
<tr>
<td>(START)-</td>
<td>RCT</td>
<td>400</td>
<td>180-540</td>
<td>PWI-DWI mismatch\textsuperscript{5}</td>
<td>Alteplase</td>
<td>90 d mRS</td>
</tr>
<tr>
<td>EXTEND\textsuperscript{7}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000Plus</td>
<td></td>
<td>4</td>
<td>1200</td>
<td>0-1440</td>
<td>MTT-DWI mismatch\textsuperscript{6}</td>
<td>None required</td>
</tr>
<tr>
<td>ITAIS-II</td>
<td></td>
<td>200</td>
<td>180-540</td>
<td>CTP-CTASI mismatch\textsuperscript{7}</td>
<td>Alteplase</td>
<td>90 d mRS</td>
</tr>
<tr>
<td>ITAIS-III</td>
<td></td>
<td>200</td>
<td>180-540</td>
<td>CTP-CTASI mismatch\textsuperscript{7}</td>
<td>Alteplase</td>
<td>90 d mRS</td>
</tr>
</tbody>
</table>

RCT (randomized controlled trial); MRA (MR angiogram); CTA (CT angiogram); PWI (MRI perfusion weighted imaging); DWI (MRI diffusion weighted imaging); MTT (mean transit time); CTP (CT perfusion); CTASI (CTA source images).\textsuperscript{5} Proximal occlusion seen on MRA or CTA. Patients with ICA occlusion or extensive early infarcts will be excluded.\textsuperscript{6} A pilot study (START-EXTEND) will include 100 patients in selected centers. After successful completion of the pilot, EXTEND will be initiated.\textsuperscript{7} Mismatch defined as >20% and >10 mL difference between Tmax thresholded to 6 seconds delay and DWI lesion volume.\textsuperscript{8} Single-center, prospective, observational study.\textsuperscript{9} Prospective, single-arm, multicenter trial.\textsuperscript{10} Mismatch defined as >20% difference between CTP and CTASI lesion volume and a CTP lesion >2 cm.

DIAS-4 is a phase III, placebo-controlled RCT which aims to confirm the efficacy and safety of intravenous desmoteplase (90 μg/kg dose) for AIS patients in the 3- to 9-hour window.\textsuperscript{162-163} Unlike previous desmoteplase trials, the use of a mismatch criterion based on MR or CT perfusion imaging has been abandoned. Major inclusion criteria include NIHSS score between 4-24, and proximal cerebral artery occlusion or high-grade stenosis on MRA or CTA. Major exclusion criteria include ICA occlusion and evidence of extensive early infarction on MRI or CT scan. The primary outcome will be 90-day mRS score. The planned enrollment is 400 patients, and expected to be completed in mid-2012.

The START-EXTEND trial is a pilot study of the planned phase III EXTEND trial.\textsuperscript{162-163} One hundred patients will be enrolled in the pilot study to receive either IV tPA (0.9 mg/kg) or placebo in a randomized fashion, after which more centers will accrue a final sample size of 400 patients. Eligibility criteria include NIHSS score between 4-26, treatment with IV tPA between 3 (or 4.5 hours per local protocol) to 9 hours after onset, and a significant penumbral pattern (PWI-DWI mismatch of >20% and ≥10 ml mismatch...
volume using Tmax thresholded to >6 second delay). Patients with a DWI lesion volume >70 ml will be excluded. The primary outcome will be 90-day mRS score 0-1.

The 1000Plus study is a single-center, prospective observational study to assess whether the prognostic value of the mismatch is dependent on time to imaging and vessel status.\textsuperscript{162,164} The study will enroll patients with AIS or transient ischemic attack within 24 hours of onset. Patients will undergo MRI/MRA with neurologic evaluation at days 1, 2 and 5-7. MRI will be performed on a 3 Tesla MR scanner, and the PWI-DWI mismatch will be assessed using MTT maps and semi-automated software. Thrombolytic treatment is permissible but not required. The primary outcome will be infarct growth between baseline and day 5-7. Planned enrollment is 1200 patients, and the estimated completion date is October 2011.

Finally, ITAIS-II and ITAIS-III are ongoing trials which will each recruit 200 patients in the 3-9 hour time window.\textsuperscript{165-166} Patients with a mismatch between CTP (penumbra) and CTA source image (core) lesion volume of ≥20% and a CTP lesion >2cm will be enrolled and treated with IV tPA (0.9 mg/kg). The primary endpoints will be 90-day mRS 0-1, ICH at 24-36 hours, and reperfusion at 24-48 hours. Comparisons will be made to published trial data using standard CT-based criteria in the 0-3 and 3-6 hour windows.

**Imaging selection for intra-arterial therapies**

There has been a marked growth in the use of endovascular revascularization therapies in recent years.\textsuperscript{167} However, there remains little evidence for improved outcomes with this approach. The only RCT to demonstrate such a benefit was the PROACT II study.\textsuperscript{168} The MERCI\textsuperscript{7} Multi MERCI\textsuperscript{169} and Penumbra Pivotal\textsuperscript{8} trials were prospective, single-arm studies of mechanical devices that used reperfusion, rather than clinical outcome, as their primary endpoints.

According to the Stroke Therapy Academic Industry Roundtable (STAIR), equipoise exists between catheter-based intervention and supportive medical care, and IA therapy should be further tested in the setting of RCTs.\textsuperscript{7} Moreover, STAIR supports the use of imaging-based penumbral selection for such extended window trials. The problem is that there is little data on the effectiveness of advanced imaging for selecting patients for IAT. To date, the major trials of IA therapy have utilized NCCT to exclude patients with extensive infarctions (e.g., greater than one-third of the MCA territory) or with significant edema and mass effect (Table 2.5).
While the true extent of the penumbra cannot be known with certainty in the clinical setting, it can be reasonably assumed that this territory is quite large in patients with PAO who present with significant neurological deficit (e.g., NIHSS >10). On average, the MCA territory and the ICA territory (ACA + MCA) constitute approximately 250-300 cm$^3$ and 400-450 cm$^3$ of brain tissue, respectively. Therefore, substantial tissue at risk is likely present even when the core infarct exceeds 100 cm$^3$ (~1/3$^{rd}$ of the MCA territory). In this setting, the benefit of penumbral salvage will be outweighed by the extensive deficit and procedural risk related to the large infarct core. This suggests that treatment response in anterior circulation PAO patients may be better predicted by...
baseline infarct size, rather than the size of the penumbra. This idea is supported by a study in which 36 patients with MCA M1 occlusions were evaluated with xenon-enhanced CT within six hours of symptom onset. The authors found that the core infarct volume (% MCA territory with CBF <8 ml/100 g/min) was an independent predictor of favorable outcome (mRS 0-1; OR 0.85; 95%CI, 0.74-0.98), while the penumbral volume (% MCA territory with CBF=8-20 ml/100 g/min) was not associated with outcome in univariate or multivariate analysis (P=0.5). In this study, the treatments were variable: 26 patients received IV and/or IA therapy, and 10 patients were not treated.

The utility of core infarct size for treatment selection in PAO is supported by multiple studies demonstrating (1) that patients with large pretreatment DWI lesions do poorly despite successful reperfusion and (2) that patients with small DWI lesions will do well largely depending on timely reperfusion. Several studies have demonstrated that PAO patients who have early extensive DWI lesions have a worse clinical course with a significantly higher risk of malignant brain swelling. Among the studies where MRI was performed within six hours of onset, DWI lesion volume thresholds of >82 cm³ (sensitivity 87%/specificity 91%) and >89 cm³ (85.7%/95.7%) optimally predicted malignant cerebral edema. Furthermore, the DEFUSE study demonstrated that acute stroke patients with early (3-6 hrs after onset) and extensive infarcts generally had poor outcomes despite early reperfusion. In this study, only one of six patients with a “Malignant profile” (DWI lesion ≥100 cm³ and/or PWI lesion ≥100 cm³ with ≥28 seconds of Tmax delay) had a favorable outcome despite early reperfusion in three patients.

Recent evidence suggests that the core infarct volume threshold for poor outcomes may be even lower than one-third of the MCA territory. Three studies have shown that baseline DWI lesion volume >70 cm³ is highly specific for poor outcomes with or without therapy. In a retrospective study of 34 patients who underwent pretreatment MRI followed by IAT, there were six patients with baseline DWI lesion size >70 cm³ (“Futile group”), all of whom had a poor 3-month outcome (mRS 3-6) despite reperfusion in three patients. Within the study population, the Futile group patients had the largest infarct growth.

For PAO patients who do not have extensive infarcts on hyperacute imaging (<6 hours), clinical and tissue outcome is strongly dependent on early reperfusion. As previously mentioned, a post-hoc analysis of DEFUSE demonstrated that PAO patients with DWI lesion volume <25 ml had marked improvement in outcomes if they underwent early reperfusion (OR, 12.5; 95% CI, 1.8 to 83.9). Similarly, among anterior circulation PAO patients treated with IAT, those with a pretreatment DWI lesion volume <70 cm³ had higher rates of good outcomes (3-month mRSS2) with early reperfusion (64%) compared with late (17%) or no (0%) reperfusion (P<0.016). Furthermore, there was
greater infarct growth in patients who underwent delayed or no reperfusion. Despite differences in the actual threshold, these studies illustrate the importance of core infarct size in shaping the clinical response to reperfusion, and suggest that PAO patients with small core infarcts may represent a target population for IAT. Further studies are needed to better define the relationship between core infarct size, early reperfusion and clinical outcome in this patient population.

The importance of baseline core infarct size in IAT-treated patients has also been demonstrated in studies using CT-based methods for infarct delineation, including NCCT (using ASPECTS classification),\textsuperscript{178-179} CTA source images\textsuperscript{180} and CTP-CBV maps.\textsuperscript{181}

Ongoing imaging studies of IAT (Table 2.6)

MR RESCUE is an ongoing phase II RCT comparing mechanical revascularization therapy using the Merci Retriever or the Penumbra Stroke System plus standard medical care versus standard medical care alone.\textsuperscript{162-163} All patients will undergo pretreatment MRI with PWI or CT perfusion imaging. The aim is to determine whether pretreatment imaging findings influence the response to IAT. Eligibility criteria include anterior circulation PAO (ICA, MCA M1 or M2 segment), NIHSS score ≥6 and procedure initiation within 8 hours from onset. The primary outcome measure is 90-day mRS score. Approximately 70 of the planned 120 patients have been accrued.

Table 2.6 Ongoing imaging trials of IAT.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type</th>
<th>N</th>
<th>Time (min)</th>
<th>Imaging criteria</th>
<th>Device</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR RESCUE</td>
<td>RCT</td>
<td>120</td>
<td>0-480</td>
<td>PWI-DWI or CTP mismatch</td>
<td>Merci Retriever and Penumbra Stroke System</td>
<td>90 d mRS</td>
</tr>
<tr>
<td>START</td>
<td>1</td>
<td>200</td>
<td>0-480</td>
<td>NCCT plus CTAS1, CTP, or DWI</td>
<td>Penumbra Stroke System</td>
<td>90 d mRS</td>
</tr>
<tr>
<td>DEFUSE II</td>
<td>1</td>
<td>100</td>
<td>0-720</td>
<td>PWI-DWI mismatch ≥1.8\textsuperscript{3} IA thrombolytic and/or mechanical therapy</td>
<td>Penumbra Stroke System</td>
<td>30 d NIHSSS</td>
</tr>
</tbody>
</table>

RCT (randomized controlled trial); PWI (MRI perfusion weighted imaging); DWI (MRI diffusion weighted imaging); CTP (CT perfusion); CTAS1 (CTA source images). \textsuperscript{3}Prospective, multicenter, single-arm trial. \textsuperscript{7}Tmax with a threshold of 6 seconds will be used. DWI must be <70ml and Tmax must be <100ml.

**The START Trial** is a phase IV, prospective single-arm study that will test whether pretreatment core infarct volume is correlated with functional outcome in patients treated with the Penumbra System.\textsuperscript{162-163} All patients will undergo NCCT as well as one advanced imaging modality for delineation of core infarct size: CTA source images, CT perfusion and MRI DWI. Inclusion criteria include anterior circulation PAO, NIHSS score >10 and presentation within 8 hours of onset. The primary outcome measures are 90-day mRS 0-2, angiographic assessment of reperfusion (TIMI/TICI scores) and
procedural serious adverse events. Approximately 70 of the planned 200 patients have been accrued.

DEFUSE 2 is a prospective single-arm study which will test whether a specified PWI/DWI mismatch can predict which PAO patients will benefit from early reperfusion via IAT. Eligibility criteria include hemorrhagic stroke with NIHSS score ≥5 and baseline MRI including DWI, PWI and MRA. The MRI findings may be used for clinical decision making. Automated software will create research maps for calculating the mismatch. A Target Mismatch will be defined as a PWI volume (Tmax >6 seconds) that is at least 1.8 times as large as the DWI volume. Furthermore, the DWI lesion must be <70 ml and the PWI lesion <100 ml. The primary endpoint will be an NIHSS improvement of at least 8 points or score of 0-1 at 30 days. Thus far, 50 of the planned 100 patients have been enrolled (personal communication, Dr. Greg Albers).

Using Imaging to assess treatment-related risk: Predictors of hemorrhagic transformation

The benefits of reperfusion therapy must be balanced against its risks, particularly post-treatment intracerebral hemorrhage (ICH). Evidence from both IV and IA studies suggests that pre-treatment neuroimaging may be able to identify patients at high risk for hemorrhagic transformation. Early ischemic changes on NCCT (e.g., loss of gray-white matter differentiation, effacement of sulci) have been associated with sICH and parenchymal hematomas, although other studies were not able to confirm these findings. MRI appears to provide a better assessment of clinically significant hemorrhage risk than NCCT. In a retrospective multicenter study of 645 patients with anterior circulation ischemic stroke treated with IV or IA thrombolysis, DWI lesion size was an independent risk factor for sICH (OR 1.080; 95%CI 1.012-1.153 per 10 ml increase). The rates of symptomatic ICH were 2.8, 7.8 and 16.1% for small (≤10 ml), moderate (10-100 ml) and large (>100 ml) DWI lesions, respectively (P<0.05). Of the study cohort, 109 (16.9%) patients underwent intra-arterial therapy. Numerous studies have confirmed this finding. Moreover, the elevated risk in patients with large DWI lesions appears to be further increased when there is subsequent reperfusion. In a post hoc analysis of the DEFUSE study, only the interaction between DWI lesion volume and reperfusion status was an independent predictor of sICH (OR 1.77; 95%CI 1.25 to 2.50 per 10 ml increase in DWI volume) when early reperfusion status was included in the model. Therefore, an acute infarct volume threshold may not only identify patients who will respond to reperfusion, but may also be used to exclude patients with an increased risk of harm from treatment.
Feasibility and practicality of advanced neuroimaging in the treatment setting

If advanced neuroimaging selection is validated for extended window therapies, there will be challenges to the implementation of these imaging protocols, particularly for MRI. While MRI has been demonstrated to be feasible in the treatment setting,191-193 multiple patient-related factors prevent imaging of all stroke patients, including contraindications to MRI, agitation, diminished consciousness and unstable medical condition.194-195 Fast imaging protocols (under 15 minutes) and head immobilization may alleviate the issues related to patient agitation and medical instability.191-192,196 Additionally, there are organizational hurdles such as scanner availability, presence of trained personnel and time delays to imaging.194 However, increased experience has been shown to facilitate logistics and decrease imaging-related delays.192 In one study, there was no significant difference in door-to-needle times between MRI and CT.193

Keeping in mind that no treatment is offered beyond three hours in the majority of medical centers, stroke MR imaging for extended window therapy would produce an increase in the number of treatable patients, despite the above-mentioned challenges. In fact, the majority of late-presenting patients (up to 85%) should be able to undergo such imaging.191,193-195 It should be acknowledged that such an approach will likely increase health care costs, although this would be justified if there is a proven clinical benefit.192

Expert commentary and five-year view

The use of time from stroke onset and noncontrast CT scans for reperfusion therapy decisions in acute ischemic stroke is likely to be supplemented by advanced neuroimaging that provides critical information on relevant brain physiology in the extended time window. However, despite the extensive number of investigations, there is no clear-cut evidence that the most widely employed advanced neuroimaging approach improves clinical outcomes. Specifically, studies of the MRI diffusion-perfusion mismatch have yielded conflicting results. It is apparent that alternative imaging criteria are needed to better identify which patients will respond to early reperfusion.

In the next five years, we believe that the mismatch hypothesis will be invalidated. Inherent flaws of the mismatch approach include its relative nature which results in a nonspecific representation of ischemic stroke physiology. We believe that approaches based on the severity of the clinical deficit, site of arterial occlusion and absolute core infarct volume will prove to be more accurate for identifying patients who will respond.
to treatment by excluding those patients who cannot be rescued (e.g., very large core infarcts) or in whom treatment will provide no further benefit (e.g., mild deficits and no visible occlusion). It is probable that such criteria will also consider the effectiveness of the treatment approach (IV vs. IA therapy). We have already incorporated these principles in our current algorithm for triaging patients to endovascular therapy (Figure 2.4).

Figure 2.4 Massachusetts General Hospital imaging algorithm for deciding which patients to treat with endovascular stroke therapy.
Key issues

- The current approach to patient selection for stroke reperfusion therapies is based on the time from stroke symptom onset. This approach is reasonable in the first 3 to 4.5 hours after stroke when substantial salvageable tissue probably exists in the majority of patients. However, it neglects the variable collateral physiology that exists between individual patients and which likely plays a critical role beyond this time window.

- Advanced neuroimaging can provide important information on the state of the brain parenchyma and of the neurovasculature, which may guide treatment outside of current time windows.

- Despite extensive studies in the setting of intravenous thrombolysis, there is no clear evidence that the MRI diffusion-perfusion mismatch can improve clinical outcomes.

- Based on recent data, alternative approaches employing absolute lesion volumes of the core infarct and of the surrounding region of hypoperfusion appear promising, but require validation.

- Limited data in the setting of intra-arterial stroke therapies suggest that the baseline core infarct volume in the presence of a major artery occlusion and severe neurological deficit (NIHSS score ≥10) may provide sufficient information for predicting treatment response.

- Major trials investigating imaging selection are ongoing and aim to validate these refined approaches.
References


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Reference annotations

The following references are (*) of interest or (**) of considerable interest.

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