In this small phase II trial, baseline DWI lesion volume <25ml was an independent predictor of excellent clinical outcome from tPA, in patients with stroke presenting 3-6 hours after onset.

Clinical Problem: *A 65 year old woman presents to the emergency department with right hemiparesis since she woke up this morning. She has been last well at the time she went to bed, which is 5 hours before. You are considering IV tissue plasminogen activator (tPA) but she is outside the recommended treatment window. Could Magnetic Resonance (MR) imaging guide your decision?*

Clinical Question:
In patients presenting with acute stroke in the 3 to 6 hour time window, does MR diffusion (DWI) or perfusion weighted (PWI) imaging predict outcome of treatment with IV tPA?

Search Strategy:
A Medline search for the terms "Stroke", "tPA" and "MRI" revealed 80 publications. Adding a filter of "Randomized controlled trials" limited results to 3. One study is the promising WAKE-UP[1] study which is yet not completed. The other 2 are related to the Phase 2 study EPITHET[2] (Effects of alteplase beyond 3hr after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial), the Ebinger et al, 2009[3]; and the Parsons et al, 2010[4].
The latter was chosen due to its most relevance to our clinical question.

Clinical Bottom Line:

Primary DWI lesion volume <25 ml may be a useful tissue based predictor for excellent functional outcome in patients treated with tPA in 3 to 6 hr time window after acute stroke .

The Evidence:
Design*: EPITHET[2] was a phase II prospective, randomized, double blinded, placebo-controlled trial of acute ischemic stroke patients imaged with serial MRI and randomized to IV tPA or Placebo at 3-6 h after symptom onset. Parsons et al[4], was a post-hoc study, which analyzed whether the volume of PWI and DWI pretreatment would predict outcome.*
Patients*: 98 patients who had both baseline PWI and DWI imaging, were randomized to tPA versus placebo.*
Inclusion Criteria: *The study included patients with acute hemispheric ischemic stroke who presented 3 to 6 h after symptom onset, were 18 years of age or older, had a National Institutes of Health Stroke Scale score of >4, and had a premorbid modified Rankin score (mRS) of less than or equal to 1.*
Exclusion Criteria: *Acute hemorrhage and major early ischemic change (defined as ischemia of more than one-third of the territory of the middle cerebral artery), standard contraindications to alteplase.*
Outcomes*: Outcome was dichotomized into excellent or poor clinical outcome at 90 days. Excellent outcome was defined as a mRS of 0-1 and poor outcome was defined as a mRS of 5-6.*

Data*:*

Table 1: Excellent vs. Poor Clinical Outcomes at 90 days Dichotomized by DWI volumes

		Univariate Analysis		Multivariate Analysis	
Pre-treatment DWI Volume	**Outcome at 90 days**	**OR (95%CI)**	**P Value**	**OR (95%CI)**	**P Value**
Acute DWI<25 ml	**Excellent outcome, mRS 0-1 (Placebo group) (n=35)**	2.7 (0.5-15.3)	0.270		
	Excellent outcome mRS 0-1 (tPA group) (n=43)	17.0 (3.1-92.4)	0.001	15.8 (2.03-99.8)	0.008
Acute DWI>25 ml	**Poor outcome, mRS 5-6 (Placebo group) (n=35)**	1.3 (0.2-9.3)	0.772		
	Poor outcome, mRS 5-6 (tPA group) (n=43)	9.9 (1.8-54.4)	0.008	1.78 (0.19-16.5)	0.313

DWI = Diffusion Weighted Imaging, tPA = tissue plasminogen activator, OR = odds ratio, mRS = modified Rankin Score

Table 2: Patients with Excellent Outcomes at 90 days in tPA vs. Placebo Groups

Outcome at 90 days	tPA	Placebo	Absolute Risk Reduction (95% CI)	Number Needed to Treat (95% CI)
Excellent Outcome mRS 0-1, acute DWI<18 ml	71% (n=21)	33% (n=18)	38% (9%-67%)	2.6 (1.5-11.3)
Excellent Outcome mRS 0-1, acute DWI<25 ml	67% (n=24)	35% (n=23)	32% (12%-52%)	3.1 (1.9-8.5)

Comments:

1) The design of this study is based on post-hoc analysis and consists of looking at the data—after the experiment has concluded—for patterns that were not specified a priori.
2) This study includes multiple statistical analyses with potential risk for Type 1 and Type 2 errors.
3) The patient population number is relatively small; EPITHET study seemed to be underpowered to test its primary endpoint.
4) There is a strong need for a phase III Trial to determine the validity of Hypotheses generated in this study. (Two RCTs currently under completion EXTEND[5] and WAKE-UP[1]).

References:

[1] Thomalla G, Ebinger M, Fiehler J, et al. WAKE-UP - Efficacy and safety of MRI-based thrombolysis in wake-up stroke. Nervenarzt 2012; 83(10):1241-51.

[2] Davis SM, Donnan GA, Parsons MW, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET). Lancet Neurol 2008; 7: 299–309.

[3] Ebinger M. Iwanaga T. Prosser JF, et al. Clinical–Diffusion Mismatch and Benefit from Thrombolysis 3 to 6 hours after acute stroke. Stroke 2009; 40(7):2572-4.

[4] Parsons MW, Christensen S, McElduff P, et al. Pretreatment diffusion- and perfusion-MR lesion volumes have a crucial influence on clinical response to stroke thrombolysis. Journal of Cerebral Blood Flow & Metabolism 2010; 30:1214–1225.

[5] Ma H1, Parsons MW, Christensen S, et al. Investigate Extending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND). Int J Stroke. 2012; 7(1):74-80.

Key Words: stroke, tPA (tissue plasminogen activator), MRI (Magnetic resonance imaging), DWI (Diffusion weighted imaging), time window

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Date Appraised: May 6th 2014.