

Desmoteplase and imaging science



Intuition and empirical observation suggest that the magnitude of benefit for any given treatment can vary according to the baseline prognosis. Patients who are initially badly affected have only a small chance of responding to therapy, whereas patients with milder symptoms will largely do well regardless of therapy. Thus, the expected magnitude of the treatment effect for any therapy can be quantitatively (or even qualitatively) modified by the prognosis (figure). Alternatively, and in my opinion most importantly in stroke, prognostic factors might be of much greater importance quantitatively than any treatment effect, such that the variance in outcomes introduced by widely differing prognoses overwhelms any chance of showing a treatment effect in a clinical trial. The inclusion of patients without vascular occlusions in the DIAS-2¹ trial published in this issue of *The Lancet Neurology* might account for the failure to show any efficacy of desmoteplase over placebo.

In stroke thrombolysis, time from symptom onset, age, stroke severity, and baseline CT imaging have been used to select patients for therapy and to identify the worst and best prognostic groups. Indeed, the ECASS-3 investigators² reported CT protocol violations of only 2.1%, implying that they were extremely successful in using CT criteria to exclude patients with large ischaemic stroke—the group with the worst prognosis. The temptation to infer from the successful thrombolytic trials that the selection criteria might be most important in later time windows after stroke onset is great, but this remains to be proven.

Many stroke experts believe that a better physiological way to select patients is to use brain imaging with multimodal MR or CT imaging. Instead of excluding patients with the worst prognosis, these techniques might provide a way to identify penumbral tissue and include patients who ought to be, by definition, the most suited to fast reperfusion. Intensive investigation globally has led to great advances in imaging technology, but our understanding of what biological processes are actually being imaged in acute stroke is incomplete, and, to date, the penumbral hypothesis has yet to be proven.

Desmoteplase is a novel recombinant tissue plasminogen activator that occurs naturally in the saliva of the Mexican vampire bat (*Desmodus rotundus*).

Desmoteplase has several pharmacological properties that make it an ideal compound to treat ischaemic stroke. The DIAS programme of studies has implicitly attempted to investigate two hypotheses simultaneously: whether desmoteplase is safe and efficacious for the treatment of stroke; and whether multimodal brain imaging can select the patients who would benefit from reperfusion. However, the second hypothesis is provable only if the first hypothesis is true.

In the DIAS-1 trial,³ desmoteplase was tested in a dose-escalation design in a 3–9 h window after the onset of ischaemic stroke. Crucially, only patients aged 85 years or younger, with a National Institutes of Health stroke scale (NIHSS) score of 4–20 points, and evidence of a visual diffusion–perfusion (DWI–PWI) mismatch greater than 20% were included in the study. DWI–PWI mismatch was defined with standard diffusion imaging and relative mean transit time (rMTT) maps. When the study was underway, an additional exclusion criterion for safety was added: patients with an infarction greater than a third of the middle cerebral artery territory on diffusion-weighted imaging (DWI) were excluded. After changing to weight-adjusted doses, the study was concluded successfully, with a suggestion of safety and a high reperfusion rate as judged by MR angiography.

During the interim, multimodal CT became more widely available, and the DIAS-2 study was designed to look at two doses of desmoteplase with either multimodal CT or MR to define tissue at risk. Patients were younger than 85 years, had to score between

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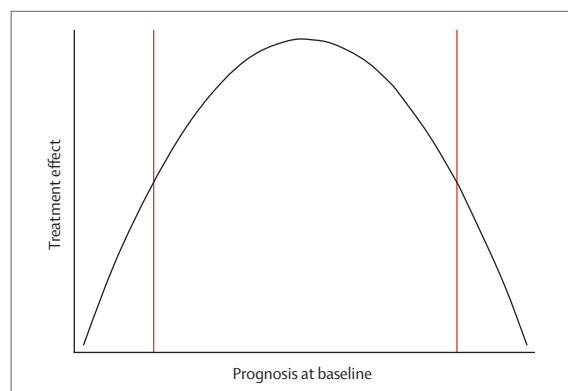


Figure: A possible model of treatment effect size

Patients with poor and good prognoses show small treatment effect sizes; the largest treatment effect is concentrated in the group with an intermediate prognosis.

4 and 24 points inclusive on the NIHSS, and had to show at least a 20% mismatch on penumbral imaging with either MR or CT. Mismatch was defined qualitatively at each site. The primary outcomes were clinical. The trial did not show a benefit of desmoteplase over placebo and despite a low rate of symptomatic haemorrhage, there was an increased rate of death in the high dose (125 µg/kg) desmoteplase group.¹

Additional data have emerged that suggest that the usual rMTT map typically overestimates the volume of tissue at risk, and more conservative assessments of the perfusion abnormality are needed.⁴⁻⁶ Benign oligoemia, although a misnomer because the tissue typically has elevated cerebral blood volume, is tissue that does not continue to infarction regardless of reperfusion and is over-represented in typical rMTT maps.^{7,8} Time-to-peak maps with a delay of 4 seconds or more might be more specific to identify tissue at risk. Thus, the estimated mismatch tissue volumes of 75–87 cm³ in DIAS-2 might have been a substantial overestimate of the true tissue at risk. Furthermore, the DWI lesion might only be a close approximation of the infarct core, but when the lesion is large, the prognosis is so poor that thrombolytic treatment is, at best, unhelpful.^{9,10}

Other restrictions of the penumbral hypothesis are theoretical and dependent on technology. CT or MR images are a single snapshot in time and might not well represent the dynamic nature of the intracranial circulation in the acute stroke setting. The snapshot in time concept also applies to current non-invasive vascular imaging with CT or MR angiography, although time-resolved CT and MR angiography is now possible. The CT perfusion technique at the time of this study only covered part of the brain. However, CT scanners that can provide full brain perfusion imaging at the same sitting are now available. MR blood flow measurements are calibrated to a PET standard and do not provide absolute estimates of blood flow. However, work on this technique continues, and as these and newer technologies permeate the clinical infrastructure, more will be known about the dynamic nature of an acute arterial occlusion and brain perfusion status.

An important point in the DIAS-2 trial design and outcome was the lack of emphasis on the blood vessel; the first target of thrombolytic therapy is the occluded vessel. The baseline rates of vessel occlusion (TIMI 0–1 points) were half of what was seen in the DIAS-1

and DEDAS trials.¹¹ We now recognise that recanalisation of the target arterial lesion might not always lead to reperfusion (the “no re-flow” phenomenon), and that owing to robust collateral circulation, substantial reperfusion can occur in the absence of recanalisation. However, in most patients with ischaemic stroke, recanalisation is a necessary precursor to recovery. The focus of thrombolytic trials must include measurement of the rate of recanalisation as a crucial secondary outcome. With the widespread use of CT angiography and, less commonly, MR angiography, this is now technologically possible. Patients’ prognosis and response to therapy can be judged by the “clot burden score”, a simple measure of the location and extent of a thrombus.¹² Not surprisingly, the clot burden score correlates well with the baseline stroke severity and the baseline Alberta Stroke Program Early CT score (ASPECTS). The absence of a target vessel occlusive lesion in most patients might have been a primary reason why DIAS-2 did not show a positive result.

Thus, although desmoteplase might yet prove to be the thrombolytic of choice, the DIAS-2 trial design forged too far ahead of the imaging science. The lessons learned must be applied to the DIAS-3 study. Importantly, vascular status will be measured non-invasively before treatment as an inclusion criterion and used as an outcome, and the DIAS-3 study will test a single hypothesis—does the drug work? We shall all look forward to a novel and improved thrombolytic drug for stroke.

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I have no conflicts of interest, but my institution plans to participate in the DIAS-3 trial.

- 1 Hacke W, Furlan AJ, Al-Rawi Y, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion–diffusion weighted imaging or reperfusion CT (DIAS-2): a prospective, randomised, double blind, placebo-controlled study. *Lancet Neurol* 2008; published online Dec 18. DOI:10.1016/S1474-4422(08)70267-9.
- 2 Hacke W, Kaste M, Bluhmki E, et al, for the ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; **359**: 1317–29.
- 3 Hacke W, Albers G, Al-Rawi Y, et al, for The DIAS Study Group. The Desmoteplase in Acute Ischemic Stroke trial (DIAS). A phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke* 2005; **36**: 66–73.
- 4 Heiss WD, Sobesky J, Hesselmann V. Identifying thresholds for penumbra and irreversible tissue damage. *Stroke* 2004; **35** (suppl 1): 2671–74.
- 5 Kane I, Carpenter T, Chappell F, et al. Comparison of 10 different magnetic resonance perfusion imaging processing methods in acute ischemic stroke: effect on lesion size, proportion of patients with diffusion/perfusion mismatch, clinical scores, and radiologic outcomes. *Stroke* 2007; **38**: 3158–64.

- 6 Davis SM, Donnan GA, Parsons MW, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurol* 2008; **7**: 299–309.
- 7 Butcher K, Parsons M, Allport L, et al, for the EPITHET Investigators. Rapid assessment of perfusion–diffusion mismatch. *Stroke* 2008; **39**: 75–81.
- 8 Butcher KS, Parsons M, MacGregor L, et al, for the EPITHET Investigators. Refining the perfusion–diffusion mismatch hypothesis. *Stroke* 2005; **36**: 1153–59.
- 9 Guadagno JV, Warburton EA, Aigbirhio FI, et al. Does the acute diffusion-weighted imaging lesion represent penumbra as well as core? A combined quantitative PET/MRI voxel-based study. *J Cereb Blood Flow Metab* 2004; **24**: 1249–54.
- 10 Albers GW, Thijs VN, Wechsler L, et al, for the DEFUSE investigators. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Ann Neurol* 2006; **60**: 508–17.
- 11 Furlan AJ, Eyding D, Albers GW, et al. Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS): evidence of safety and efficacy 3 to 9 hours after stroke onset. *Stroke* 2006; **37**: 1227–31.
- 12 Puetz V, Dzialowski I, Hill MD, et al, for the Calgary CTA Study Group. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the Clot Burden Score. *Int J Stroke* 2008; **3**: 230–36.