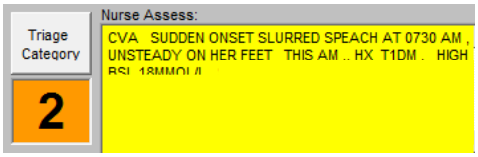
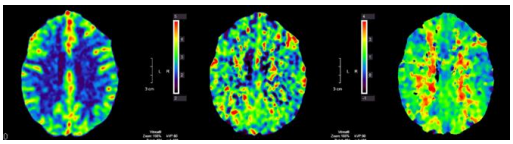
Clinical update no. 518
25 July 2018

There a lot of new stroke trials – they are mostly directed at expanding the indications for thrombolysis and thrombectomy. Your stroke team has most likely read them. Should they change practice?



48yr-F, diabetic. History clarified she had symptoms on waking, with slurred speech, weakness and incoordination of left arm and leg. Could she be a candidate for thrombolysis when time last normal is not known?



CT perfusion imaging suggested asymetery and possible ischaemia in the left frontal lobe.

The NEW ENGLAND JOURNAL of MEDICINE

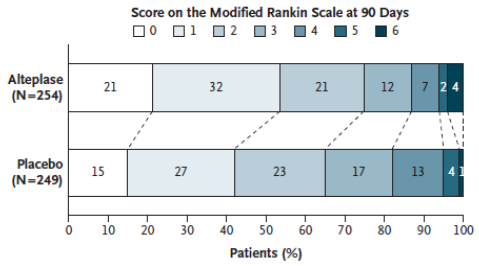
ORIGINAL ARTICLE

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

for the WAKE-UP Investigators*

This article was published on May 16, 2018, at NEJM.org.

The study enrolled stroke patients with unknown time of onset, where MRI imaging suggested recent cerebral infarction likely to be within 4.5hr. Funding ran out after enrolling 503 of a planned 800 patients. Primary outcome was an mRS 0-1at 90 days (no or minimal deficit), with a good outcome in 53% with alteplase v 42% control, p 0.02.



mRS 0-1

53% with alteplase v 42%, p 0.02

Deaths

4.1% v 1.2%, p 0.07

Symptomatic intracranial haemorrhage

2.0 v 0.4%, p 0.15

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Variable	Alteplase Group (N=254)	Placebo Group (N=249)
Median NIHSS score (IQR)†	6 (4–9)	6 (4–9)
Median lesion volume on diffusion-weighted imaging (IQR) — ml	2.0 (0.8–7.9)	2.5 (0.7–8.8)
Median time from symptom recognition to treatment initiation (IQR) — hr	3.1 (2.5–3.8)	3.2 (2.6–3.9)
Interval between last time that the patient was last known to be well and treatment initiation (IQR) — hr	10.3 (8.1–12.0)	10.4 (8.1–12.1)

Table 2. Primary and Secondary Efficacy Outcomes (Intention-to-Treat Population).*

Outcome	Alteplase Group (N=254)	Placebo Group (N=249)	Effect Variable	Adjusted Value (95% CI)†	P Value
Primary efficacy end point					
Favorable outcome at 90 days — no./total no. (%)‡	131/246 (53.3)	102/244 (41.8)	Odds ratio	1.61 (1.09 to 2.36)	0.02
Median infarct volume at 22–36 hr (IQR) — ml¶¶	3.0 (0.8 to 17.7)	3.3 (1.1 to 16.6)	Mean difference ($\log_e$)	−0.16 (−0.47 to 0.15)	0.32¶

The strokes were mild, with median NIHSS score 6. There was no benefit for an NIHSS score >10. Despite a favourable ischaemic penumbra indicating salvagable brain, there was no difference in final infarct volume; 3.0 v 3.3 ml, p 0.32. There were more symptomatic ICH and deaths with alteplase.

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

MRI-Guided Intravenous Alteplase for Stroke — Still Stuck in Time

Essentially it is a study of wake up strokes

the results may not apply to patients who undergo only CT perfusion

It is important that clinical equipoise be maintained so that confirmatory trials can be performed.

The editorial was not supportive of thrombolysis for stroke when time of onset is unknown.

Verdict: await better evidence, though some units have implemented this already.

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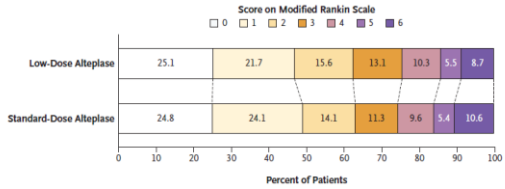
Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke

for the ENCHANTED Investigators and Coordinators*

This trial compared low dose alteplase 0.6 mg/kg v standard dose 0.9 mg/kg. It involved predominantly Asian patients. It did not show noninferiority for low-dose alteplase. There were significantly fewer symptomatic ICH with low-dose alteplase, and fewer deaths. There was essentially the same number with good outcomes, i.e.mRS 0-2. [This assumes that standard dosing improves outcomes].



Clinical Guidelines for Stroke Management 2010
National Stroke Foundation

ABSOLUTE CONTRAINDICATIONS:

1. Uncertainty about time of stroke onset (e.g. patients awaking from sleep).

3. Only minor stroke deficit which is rapidly improving.

Times change. A minor deficit with was once an absolute contraindication.

Research

JAMA | Original Investigation

Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits
The PRISMS Randomized Clinical Trial

for the PRISMS Investigators JAMA. 2018;320(2):156-166.

More than half of patients have minor neurologic deficits at presentation (NIHSS score of 0-5) and non-disabling deficit (judged as whether or not the deficit would impair function if it persisted). There can be early deterioration after a mild stroke. Trials of alteplase included few of these patients.

N = 313; median NIHSS score 2; randomised to alteplase or aspirin within 3 hours of onset; trial stopped early.

Favourable outcome (mRS 0-1)

- 78% with alteplase v 81.5%

Symptomatic ICH in 3.2 v 0%.

Intravenous Alteplase for Mild Nondisabling Acute Ischemic Stroke
A Bridge Too Far?

intravenous alteplase appears unlikely to meaningfully improve functional outcome in patients with mild ischemic stroke with initial NIHSS scores of 5 or lower and with nondisabling deficits,

Risk of symptomatic ICH with alteplase is still 2 - 3%. This trial showed no benefit from alteplase for minor stroke.

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Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA

the POINT Investigators*

N = 4881 with minor stroke or high risk TIA; randomised to clopidogrel (600mg then 75mg/day) plus aspirin (50-325mg) or aspirin alone. Primary outcome was composite of ischemic stroke, MI or death from ischaemic event at 90 days. Terminated early.

Major ischemic events in 5.0% with dual therapy v 6.5%; hazard ratio 0.75; P 0.02); with most events occurring in the first week. The benefit was confined to reduced ischaemic stroke (4.6 v 6.3% p 0.01), and no benefit if included major haemorrhage.

Major haemorrhage in 0.9% v 0.4%, p 0.02, though few were ICH, and occoured later.

Antiplatelet Therapy after Ischemic Stroke or TIA

Of note, high risk patients were excluded - cardiac source e.g. AF (need anticoagulation), severe carotid stenosis (need endarterectomy/ stent), or severe intracranial atherosclerosis (given dual therapy and not enrolled); prior cerebral bleed was an exclusion.

Risk: benefit may be optimal with dual therapy for 3 weeks, then monotherapy, with adherence to exclusion criteria.

These updates are a review of current literature at the time of writing and are the views of Dr Brendon Smith, FACEM. They do not replace local treatment protocols and policy. They may become outdated over time.