# Clinical update no. 537
# 15 May 2019

Narrative reviews

Advances in stroke medicine

*MJA* 6 May 2019

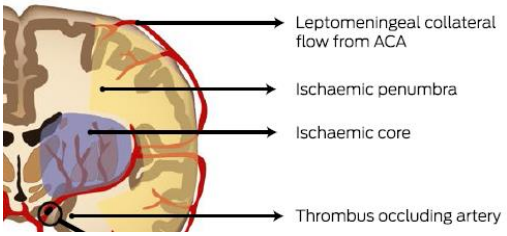
https://www.mja.com.au/journal/2019/210/8/advances-stroke-medicine

Some concepts highlighted as follows:

"tissue clock" may replace "time clock"

protocols for stroke need to include computed tomography (CT) perfusion scan and CT angiography as routine,

Although ischaemia will infarct brain tissue in a short time, an ischaemic penumbra may be salvagable with reperfusion over a longer time frame. Collateral circulation may keep tissue viable for several hours, however will eventually fail. The theory is that where perfusion imaging shows a small core infarct with surrounding ischaemic but potentially viable brain tissue then reperfusion may prevent progression to infarction, and the initial deficit may recover. The window for thrombolysis or thrombectomy is based on perfusion characteristics and not time.




Initial trials were not encouraging.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke

N ENGL J MED 368;10 NEJM.ORG MARCH 7, 2013

A favorable penumbral pattern on neuroimaging did not identify patients who would differentially benefit from endovascular therapy for acute ischemic stroke, nor was embolectomy shown to be superior to standard care.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke

for the Interventional Management of Stroke (IMS) III Investigators

Better reperfusion with thrombectomy did not give better clinical outcomes in early trials. Further thrombectomy trials did show benefit.

## Reperfusion therapies for ischaemic stroke

Ongoing trials provide data on the role of reperfusion with thrombolysis beyond the current 4.5hr window, and thrombectomy up to 24hr from onset.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 9, 2019 VOL. 380 NO. 19

Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke

for the EXTEND Investigators*

The EXTEND trial randomised patients who had hypoperfused but salvageable brain detected on automated perfusion imaging (MRI or CT) if onset between 4.5 – 9hr or on waking, comparing alteplase to placebo. Two thirds of those enrolled had "wake-up" stroke.

The primary outcome was mRS 0-1 at 90 days, i.e. functional independence.

Enrolment was stopped early at n = 225 after results from the WAKEUP trial gave a loss of equipoise, i.e. randomisation to placebo was no longer considered ethical.

There was mRS at 90 days in 35% with alteplase v 29% (ARR 1.44; 95CI 1.01 - 2.06; P = 0.04); symptomatic ICH in 6.2% v 0.9%, and death in 11.5 v 8.9%.

The authors conclude: "*Because of the limited power of our conclusions as a result of premature termination of the trial and the lack of a significant between-group difference in the secondary outcome of functional improvement *, further trials of thrombolysis in this time window are required*".

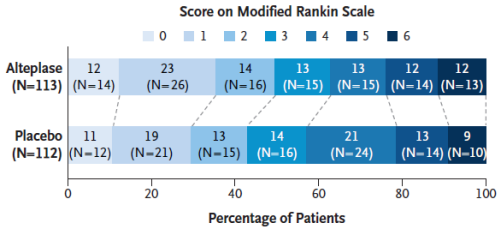



Figure 1. Scores on the Modified Rankin Scale at 90 Days.

Table 1. Characteristics of the Patients at Baseline.*

| | Alteplase (N=113) | Placebo (N=112) |
|---|---|---|
| Median NIHSS | 12 | 10 |
| Time from stroke onset to randomisation (%) | | |
| 4.5-6hr | 35 | 35 |
| Awoke with symptoms | 65 | 65 |
| Door – treatm. (median/min) | 124 | 127 |
| Large vessel occlusion (%) | 78 | 81 |
| **Outcomes.*** | | |
| mRS 0-1, 90 days - % | 35 | 29 |
| % reperfusion, 24hr | | |
| ≥90% | 50 | 28 |
| ≥50% | 72 | 52 |
| Symptomatic ICH within 36h, % | 6.2 | 0.9 |
| Major improvement, 90 d. - reduction NIHSS ≥8 or mRS 0-1 | 58 | 49 |

* Functional improvement (mRS improved by ≥1 at 90d) 95% CI – Adjusted 0.96 – 2.49; Unadjusted 0.74 – 1.87

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

**Image-Guided Intravenous Alteplase for Stroke — Shattering a Time Window**

N ENGL J MED 380;19 NEJM.ORG MAY 9, 2019

The era of time-based treatment with intravenous alteplase in patients with acute stroke may finally be drawing to a close.

The battle cry of "Time is brain!" reigned unopposed, until now. Up to 50% of patients with large-vessel occlusions have infarct cores that grow slowly, probably because of collateral flow in the penumbra.

The current trial by Ma et al. will need to be validated. It was stopped early owing to the publication of results of another clinical trial,

Trials comparing thrombolysis with thrombectomy in the late time window are warranted. Tenecteplase compares favourably to alteplase prior to thrombectomy.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 26, 2018 VOL. 378 NO. 17

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

for the EXTEND-IA TNK Investigators*

CONCLUSIONS

Tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase among patients with ischemic stroke treated within 4.5 hours after symptom onset.

Stroke FOUNDATION

Clearly no such caution here.

**Australian study will change the way stroke is treated around the world**

Published: May 07, 2019

" … *the initial window of 4.5 hours … could now be pushed to 9 hours*".

The summary exagerated the benefit, citing 44% improved outcome, rather than the absolute difference of 6% with NNT 16.

Professor Donnan said the results were likely to change treatment guidelines and practice. Curious, given that as author he emphasised "*the lack of a significant between-group difference"* and the need for further trials.

An unsual situation where the Stroke Foundation misrepresents and exagerates the study findings and then writes the Guidleines.

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 was of 'wake-up" stroke with unknown time of onset. Strokes were mild with median NIHSS 6 (range 4-9). There was mRS 0-1 at 90 days in 53% v 42%, p = 0.02, ARR 9, NNT 11. but no difference in eventual infarct volume. The editorial: "*it is important that clinical equipoise be maintained*".