Are we ready for perfusion imaging guided thrombolysis of wake-up strokes?

Doran Drew¹ · Michel Shamy^{2,3} · Debra Eagles^{1,3}

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Ratings: *Methods*—4/5, *Usefulness*—3/5

Introduction

Strokes with unknown time of onset, such as wake-up strokes, account for 15–25% of all strokes and currently have limited treatment options [2]. The authors sought to evaluate the effectiveness and safety of perfusion-imaging-guided administration of alteplase to strokes of unknown duration.

Methods

An individual patient data systematic review and meta-analysis of randomized trials comparing perfusion-imaging (perfusion-diffusion MRI, MRI with DWI-FLAIR, or perfusion CT)-guided thrombolysis with IV alteplase in adult patients with strokes of unknown time of onset, as compared with placebo or standard of care, was conducted. The study was registered with PROSPERO and followed PRISMA guidelines.

Primary outcome: good functional outcome [modified Rankin Scale (mRS) 0–1] at 90 days.

Safety outcomes: death, severe disability [mRS 4–6] or death, and symptomatic intracranial hemorrhage.

Secondary outcomes: independence [mRS 0–2] at 90 days and mRS shift towards better functional outcomes.

Main results

The authors screened 249 abstracts and found 4 RCTs (WAKE-UP, EXTEND, THAWS and ECASS-4) with a total of 843 individuals eligible for analysis.

✉ Doran Drew
dodrew@toh.ca

¹ Department of Emergency Medicine, The Ottawa Hospital, University of Ottawa, 1053 Carling Avenue, F-Main, Room EM-206, Box 227, Ottawa, ON, Canada

² Department of Medicine (Neurology), The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada

³ The Ottawa Hospital Research Institute, Ottawa, ON, Canada

	Alteplase (<i>n</i> = 429)	Control (<i>n</i> = 414)	ARR	NNT/NNH	Adjusted odds ratio (95% CI)*	<i>P</i> value
Primary outcome						
mRS 0–1 at 90 days	199/420 (47%)	160/409 (39%)	8%	NNT 12	1.49 (1.10–2.03)	0.011
Secondary outcomes						
mRS shift to improved functional outcomes at 90 days	–	–	–	–	1.38 (1.05–1.80)	0.019
mRS 0–2 at 90 days	273/420 (65%)	239/409 (58%)	7%	NNT 14	1.50 (1.06–2.12)	0.022
Safety outcomes						
Death at 90 days	27 (6%)	14 (3%)	– 3%	NNH 33	2.06 (1.03–4.09)	0.04
mRS 4–6 at 90 days	90/420 (21%)	102/409 (25%)	4%	NNT 25	0.76 (0.52–1.11)	0.15
Symptomatic ICH	11 (3%)	2 (<1%)	– 3%	NNH 33	5.58 (1.22–25.5)	0.024

ARR absolute risk reduction, NNT number needed to treat, NNH number needed to harm

*Odds ratios were adjusted for age and baseline symptom severity

Appraisal

Strengths

Exhaustive search strategy.
Search terms reported and reproducible.
Adherent to PRISMA guidelines.
Applied modified Cochrane risk of bias tool—found low risk of methodologic bias.

- Low heterogeneity between included studies highlights that literature is amenable to meta-analysis.
- Individual patient data meta-analysis minimizes the impact of trials being stopped early and having overstated effect sizes which skew results.
- Patient-centered outcomes evaluated (particularly notable is the composite outcome of mRS 4–6 as a safety outcome which highlights that for our patients severe disability/dependence is not necessarily ‘better’ than death, as the mRS would suggest).

Limitations

Two trials were industry sponsored.

- All included trials were stopped, either due to loss of funding or loss of perceived “ equipoise”, possibly introducing selection bias.
- 85% of perfusion imaging used was MRI, reducing applicability to locations without capacity for widespread MRI of wake-up strokes.

Context

Time-from-symptom onset or last seen well has been our best surrogate for viable brain tissue in acute ischemic stroke for 30 years. In the view of our local stroke neurologist colleagues, the fundamental importance of this trial is the: confirmation of the superiority of tissue imaging over time windows for patient selection, affirmation of patients who may benefit from thrombolysis beyond traditional time windows, and provision of imaging-based guidance for patient selection. This meta-analysis highlights that perfusion imaging may allow us to better tailor therapy, and specifically to offer treatment to patients for whom no option would otherwise have been available.

Bottom line

The authors evaluated the role of perfusion-imaging-facilitated thrombolysis for stroke patients with unknown time of onset. They found that perfusion-imaging-guided thrombolysis could improve neurological outcomes in patients presenting with strokes without a clear time of onset. This study consolidates the existing perfusion imaging data, and hints at a future where we have more options available to our patients with wake-up strokes. Emergency physicians need to be aware of this technology, as it is likely to disrupt traditional stroke pathways, and its implementation will require forethought and planning to provide our patients the best possible care.

Declarations

Conflict of interest The authors of this manuscript have no conflicts of interest to declare.

2. Rubin MN, Barrett KM. What to do with wake-up stroke. *Neurohospitalist*. 2015;5(3):161–72. <https://doi.org/10.1177/1941874415576204>.

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