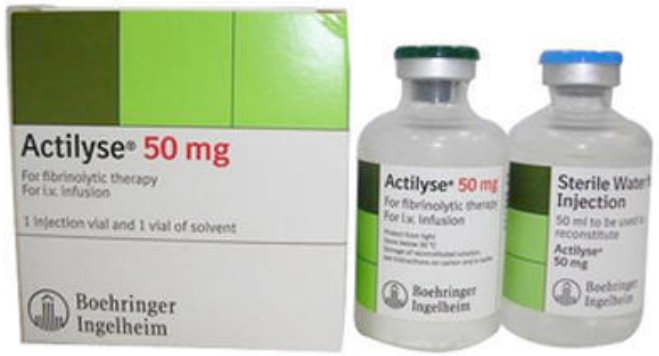
EXTENDED TIME WINDOW FOR THROMBOLYSIS

To infinity and beyond ?



Lindsay Vogel (MD)
Datablitz 2020

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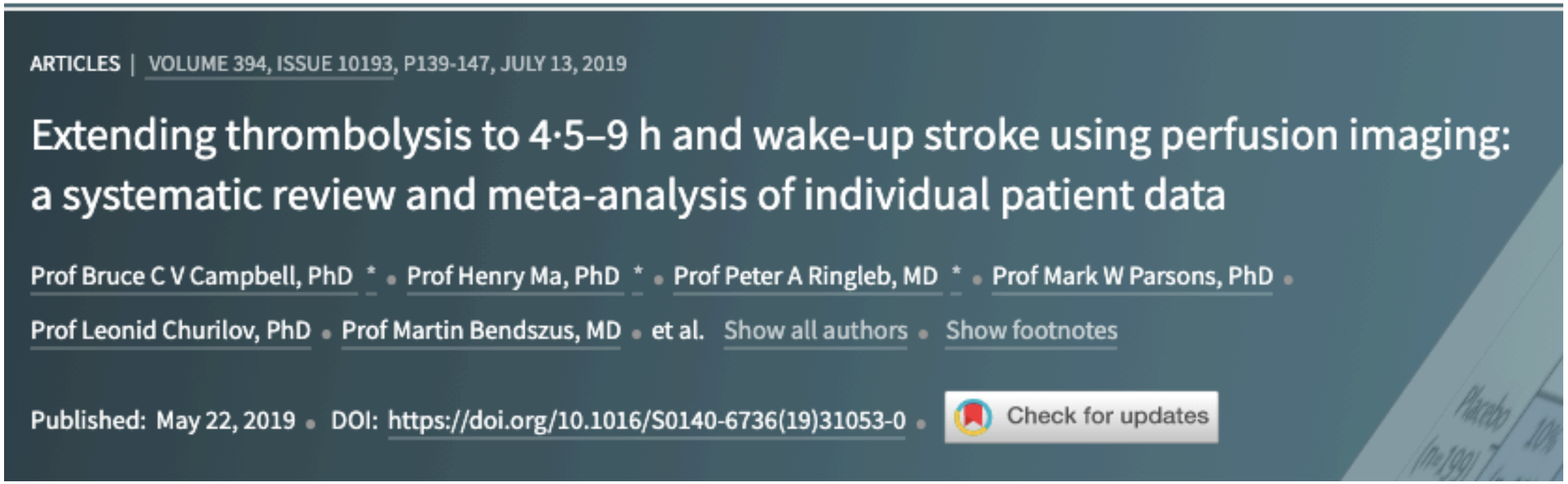
THE LANCET



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Extending thrombolysis to 4·5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data

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STATE OF THE ART

AHA/ASA Guideline

3.5.2. Time Windows	COR	LOE
1. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in Table 8 to determine patient eligibility.	I	A
2. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in Table 8 to determine patient eligibility.	I	B-R
3. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) administered within 4.5 hours of stroke symptom onset in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 hours from last known well or at baseline state and who have DWI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR.	IIa	B-R

AND AFTER 4,5H ?

Emberson et al., Lancet 2014

- Meta-analysis of 9 RCT : NINDS, ECASS I-II-III, ATLANTIS A et B, EPITHET, IST 3
- 6756 patients
- OR de 1,15

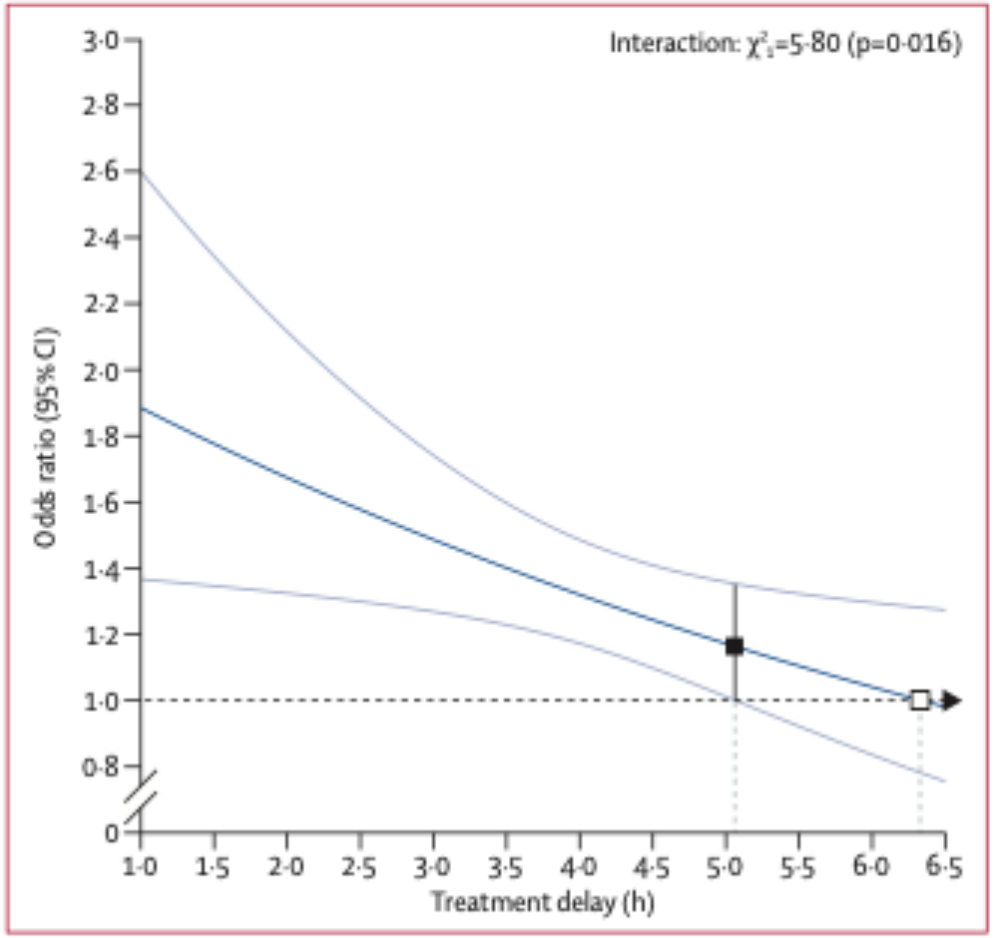

Figure 1: **Effect of timing of alteplase treatment on good stroke outcome (mRS 0–1)**

Extending thrombolysis to 4·5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data

- **Meta-analysis of individual patient data**
  - EXTEND
  - ECASS 4 EXTEND
  - EPITHET

- **Primary outcome :** excellent functional outcome (mRS score 0–1 [return to all usual activities]) at 3 months, adjusted for pretreatment clinical severity (NIHSS score) and age.

	Placebo (n=201)	Alteplase (n=213)	Odds ratio* (95% CI)	p value
Primary outcome				
Excellent functional outcome (mRS score 0–1) at 3 months	58/199 (29%)	76/211 (36%)	1·86 (1·15–2·99)	0·01
Secondary outcomes				
Functional improvement in mRS score at 3 months†	NA	NA	1·60 (1·12–2·27)	0·009
Functional independence (mRS score 0–2) at 3 months	87/199 (44%)	103/211 (49%)	1·74 (1·08–2·81)	0·02
Early neurological improvement at 72 h‡	31/197 (16%)	58/206 (28%)	2·54 (1·51–4·27)	<0·0001
Safety outcomes				
Death at 3 months	18/201 (9%)	29/213 (14%)	1·55 (0·81–2·97)	0·19
Symptomatic intracerebral haemorrhage§	1/201 (<1%)	10/213 (5%)	9·70 (1·23–76·55)	0·03

Data are n/N (%). mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. NA=not applicable. *Adjusted for baseline age and NIHSS. †Reduction of ≥1 point in mRS score (with mRS categories 5 and 6 merged), analysed using ordinal logistic regression. ‡Reduction of ≥8 points on NIHSS or reaching NIHSS score 0–1 at 72 h. §Within 36h of treatment.

***Table 2:* Study outcomes in all patients**

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	Placebo (n=152)	Alteplase (n=152)	Odds ratio (95% CI)*	p value
Primary outcome				
Excellent outcome (mRS score 0–1) at 3 months	39/151 (26%)	55/152 (36%)	2·06 (1·17–3·62)	0·012
Secondary outcomes				
Functional improvement in mRS score at 3 months†	NA	NA	1·68 (1·11–2·53)	0·014
Functional independence (mRS score 0–2) at 3 months	60/151 (40%)	77/152 (51%)	2·22 (1·25–3·94)	0·006
Early neurological improvement at 72 h‡	26/152 (17%)	44/148 (30%)	2·26 (1·26–4·03)	0·006
Safety outcomes				
Death at 3 months	16/152 (11%)	20/152 (13%)	1·28 (0·60–2·73)	0·52
Symptomatic intracerebral haemorrhage§	1/152 (1%)	7/152 (5%)	7·29 (0·88–60·18)	0·07

Data are n/N (%). mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. NA=not applicable. One patient in the placebo group did not have available mRS data at 3 months and thus was excluded from the analysis of the primary outcome and selected secondary outcomes. *Adjusted for baseline age and NIHSS. †Reduction of ≥1 point in mRS score (with mRS categories 5 and 6 merged), analysed using ordinal logistic regression. ‡Reduction of ≥8 points on NIHSS or reaching NIHSS score 0–1 at 72 h. §Within 36 h of treatment.

***Table 4*: Study outcomes in patients with automated perfusion mismatch (n=304)**

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LIMITATIONS :

- **Early termination** of two of the three included trials (EXTEND and ECASS4 EXTEND), resulting in a small sample size.

- Trials were done **before the publication of DAWN and DEFUSE**. The combined use of thrombolysis and endovascular thrombectomy in an extended time window is currently being investigated in an ongoing trial (TIMELESS).

- No **statistical interaction** between automated perfusion mismatch and treatment effect for the primary outcome (p = 0.43)

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TAKE HOME MESSAGE :

- Promising data : stroke thrombolysis in a late treatment window (>4,5 h from stroke onset), in a very selected group of patients based on perfusional imaging, seems to be safe and effective.
- Approach based on perfusional mismatch would expand the t-PA treatment window
- t-PA could be given before transfer to comprehensive stroke centers for thrombectomy

BUT the role of perfusional imaging in stroke treatment requires further study

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