Intravenous Thrombombolysis in Stroke Patients with Unknown Time of Onset –

Results of the Multicentre, Randomized, Double-blind, Placebo-Controlled WAKE-UP Trial

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on behalf of the WAKE-UP Investigators

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Disclosures

- WAKE-UP has received funding by the European Union Seventh Framework Programme
- There was no industry funding or involvement in any aspect of the trial

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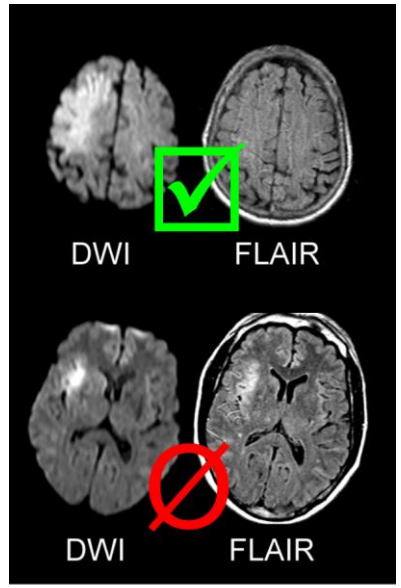
Aim and Design

- **Aim**: To prove efficacy and safety of MRI-based thrombolysis in patients with unknown time of symptom onset
- **Design**: randomised, placebo-controlled clinical trial (Alteplase vs. Placebo 1:1)
- **Planned sample**: 800 ischemic stroke patients (unknown symptom onset)
- **Inclusion criteria**:
  - Acute stroke with unknown symptom onset, disabling neurological deficit
  - Last known well >4.5 hours (ie not eligible for IV alteplase by licence)
  - Age 18-80 years
  - Treatment can be started within 4.5 h of symptom recognition
  - Written informed consent
  - MRI completeted and indicative of lesion age ≤4.5 h: “DWI-FLAIR-mismatch”
- **Exclusion criteria**:
  - Planned thrombectomy
  - Any contradindication against treatment with alteplase (except for unknown time window)



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Study Procedures and Results

- **Randomization:** Randomization in 1:1 ratio (alteplase or placebo), stratified according to age (≤60 / >60 years) and symptom severity (NIHSS score ≤10 / >10)
- **Treatment:** Alteplase 0.9 mg per kilogram of body weight (with 10% as bolus, the remainder by infusion over 60 minutes) or matching placebo
- **Follow-up:** MRI at 22-36 hours to detect intracranial hemorrhage and to assess infarct volume; Clinical follow-up at 22-36 hours, 5-9 days, and 90 days after stroke
- **End of the trial:** Enrolment stopped on June 30, 2017 at Steering Committee decision based on anticipated cessation of funding from the European Union
- **503 patients were randomized: 254 assigned to receive alteplase and 249 to receive placebo**

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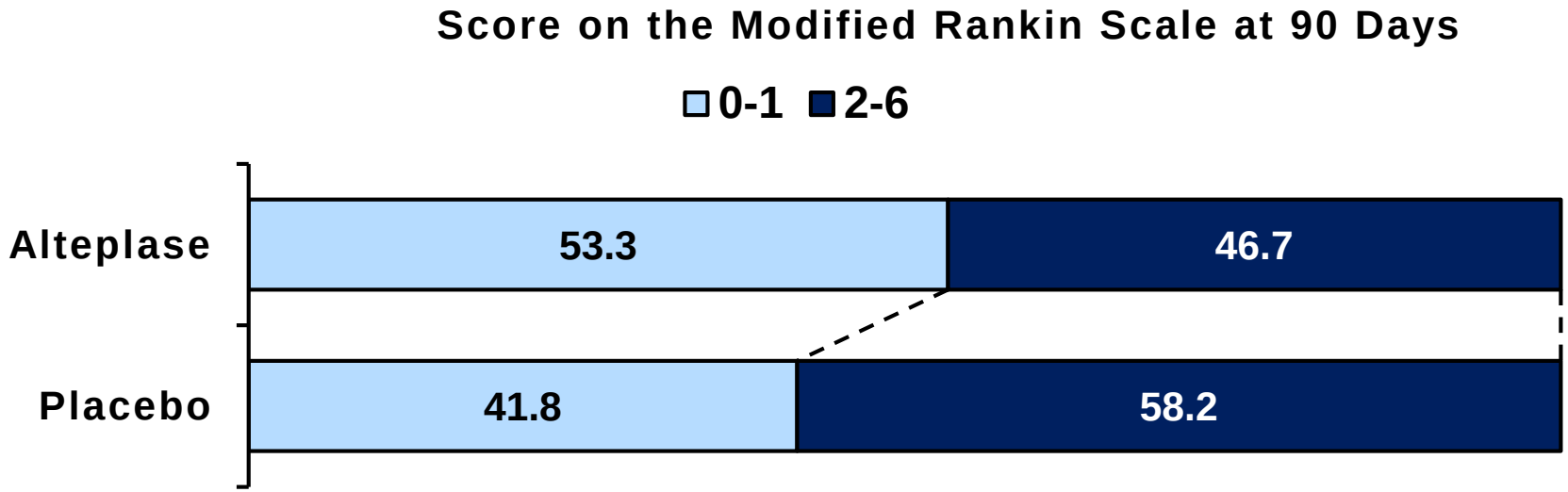
Primary Endpoint



Endpoint	Alteplase (n=254)	Placebo (n=249)	Effect Variable	Adjusted Value (95% CI) *	P-Value
Favorable outcome (mRS 0-1) at 90 days	131/246 (53.3%)	102/244 (41.8%)	Odds ratio	**1.61 (1.09-2.36)**	**0.02**

** Adjusted for age and NIHSS at baseline*

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Selected Secondary and Safety Outcomes

- Secondary efficacy endpoint: mRS “shift analysis”

Endpoint	Alteplase (n=254)	Placebo (n=249)	Effect Variable	Adjusted Value (95% CI) *	P-Value
Median mRS score at 90 days („shift analysis“)	1 (1-3)	2 (1-3)	Common odds ratio	**1.62 (1.17-2.23)**	**0.003**

- Safety endpoints:

Endpoint	Alteplase	Placebo	Adjusted Odds Ratio (95% CI) *	P-Value
Death at 90 days	4.1%	1.2%	3.38 (0.92-12.52)	0.07
Symptomatic intracranial hemorrhage as defined in SITS-MOST	2.0%	0.4%	4.95 (0.57-42.87)	0.15
Parenchymal hemorrhage type 2 (PH-2)	4.0%	0.4%	**10.46 (1.32-82.77)**	**0.03**
Any serious adverse event (SAE)	22.3%	21.3%		0.83

** Adjusted for age and NIHSS at baseline*

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Conclusions

- In patients with unknown symptom onset stroke with MRI pattern of DWI-FLAIR-mismatch, treatment with alteplase resulted in better functional outcome than placebo.
- Consistent benefit across all categories of outcome and major clinical secondary endpoints.
- Effect size of MRI-guided thrombolysis in unknown symptom onset stroke is comparable to effect size of thrombolysis <4.5 hours.
- Numerically higher rates of symptomatic intracranial hemorrhage and trend towards higher mortality with alteplase, which might have become significant with larger sample size.
- Paradigm change: first positive trial of intravenous thrombolysis relying on patients selection by advanced brain imaging without information on time of symptom onset.
- MRI-guided intravenous thrombolysis represents an effective treatment option for stroke patients with unknown symptom onset, especially for those with minor or moderate stroke who are not eligible for mechanical thrombectomy.

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