Waking Up to and EXTENDed Window: A New TWIST on Patient Care

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My disclosure

- Co-chief investigator in Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST)

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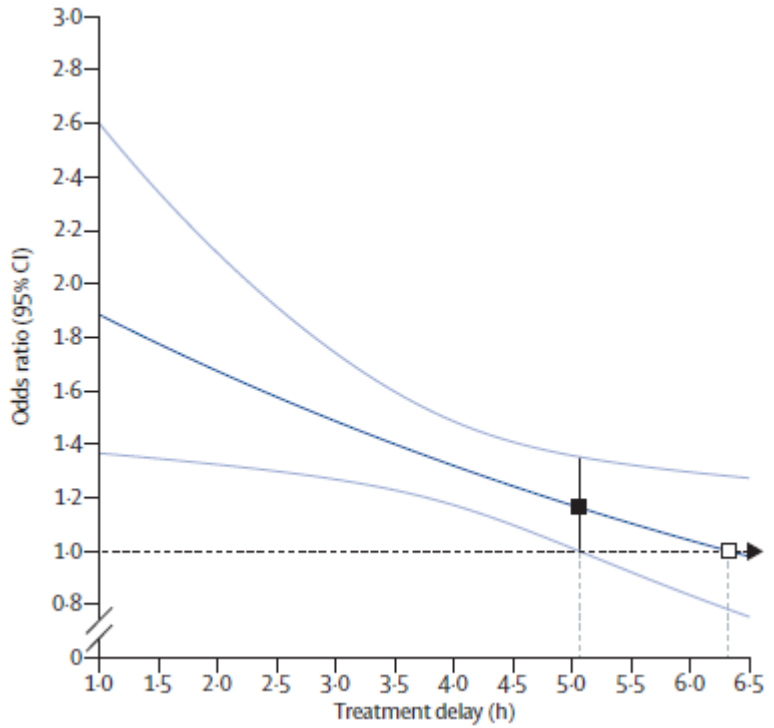
Thrombolytic treatment in **stroke within 4.5 hours of onset**

- Thrombolytic treatment **recommended**



Emberson J. *Lancet* 2014

Thrombolytic treatment in **wake-up stroke**

- Thrombolytic treatment **not recommended**
- **20%** of patients with acute ischaemic stroke
- Stroke onset is probably **close to time of awakening**: Clinical and radiological characteristics are similar to those of patients with known stroke duration <4.5 hours

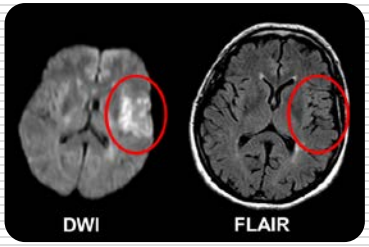
Thrombolytic treatment in wake-up stroke: **Two strategies**

A. Treatment of **patients selected with advanced imaging** (WAKE-UP, THAWS and EXTEND and ECASS-4 trials)

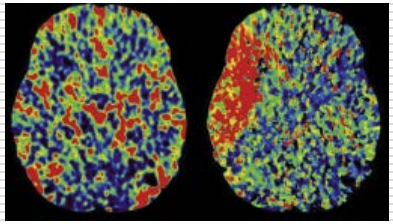
B. Treatment of **patients within 4.5 hours of wake-up**, without use of advanced imaging (TWIST)

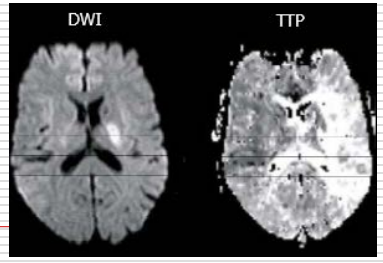
Strategy A: Treatment based on **imaging selection**

- ***«Recent infarction»***
  - MRI DWI/FLAIR mismatch
    (WAKE-UP and THAWS trials)



- ***«Penumbra»***
  - CT- or MRI-perfusion core/penumbra mismatch
    (EXTEND and ECASS-4 trials)





WAKE-UP trial: positive

- Alteplase vs. placebo in 503 patients with wake-up stroke, symptom duration >4,5 hours, and **DWI/FLAIR mismatch**
- Good functional outcome: **OR 1.6** (1.1-2.4), p=.02
- Symptomatic ICH: OR 10 (1.3-83), p=.03

Thomalla G. *NEJM* 2018;379(7):611-22

THAWS: Neutral

- Alteplase 0.6 mg/kg vs. placebo in 131 patients with wake-up stroke, duration >4,5 hours, and **DWI/FLAIR mismatch**
- Good functional outcome: **RR 1.0** (0.7-1.4) p=.9
- Symptomatic ICH: 1 vs. 0 patients

Koga M. Presentation at ESOC, May 2019

EXTEND trial: Positive

- Alteplase vs. placebo in 225 patients with duration 4.5-9 hours (65% with wake-up stroke), and with **CT- or MRI-perfusion core/penumbra mismatch**
- Good functional outcome: **RR 1.4** (1.0-2.1), p=.04
- Symptomatic ICH: RR 7.2 (1.0-53), p=.05

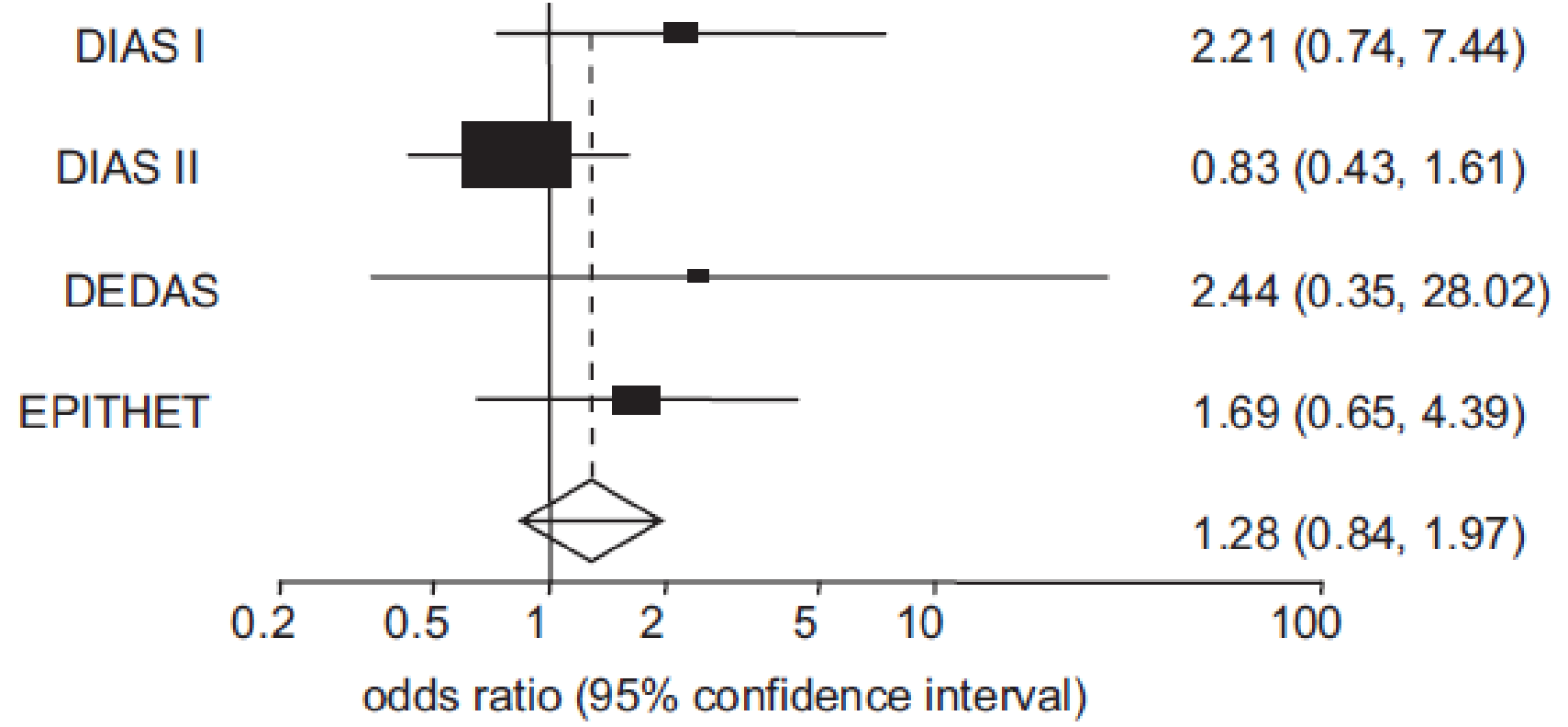
Ma H. *NEJM* 2019;380:1795-803

ECASS-4: Neutral

- Alteplase vs. placebo in 119 patients with duration 4.5-9 hours (69% with wake-up stroke), and with **MRI- perfusion core/penumbra mismatch**
- Good functional outcome: **OR 1.2** (0.6-2.3), p=.6
- Symptomatic ICH: 1 vs. 0 patients

Ringleb P. *IJS* 2019. DOI: 10.1177/1747493019840938

Other trials using advanced imaging in extended time window (4.5-9 hours)



Mishra NK. *Stroke* 2010; 41:e25-e44

Summary - Treatment based on **imaging selection** (strategy A)

- MRI DWI/FLAIR mismatch, and CT- or MRI-perfusion core/penumbra mismatch, seem to identify patients who benefit

- Positive findings from WAKE-UP and EXTEND trials need to be confirmed in more trials

Strategy B: Treatment **<4.5 hours of wake-up,** without advanced imaging

- The **majority** of patients have no mismatch, or no access to advanced imaging
- Treatment effect is **plausible**
  - Stroke onset is close to time of wakening
  - Clinical and radiological characteristics are similar to those of patients with known stroke duration <4.5 h
  - Strong findings in WAKE-UP and EXTEND trials
- Yet, **no other studies** using this strategy, and no comparisons of the two strategies

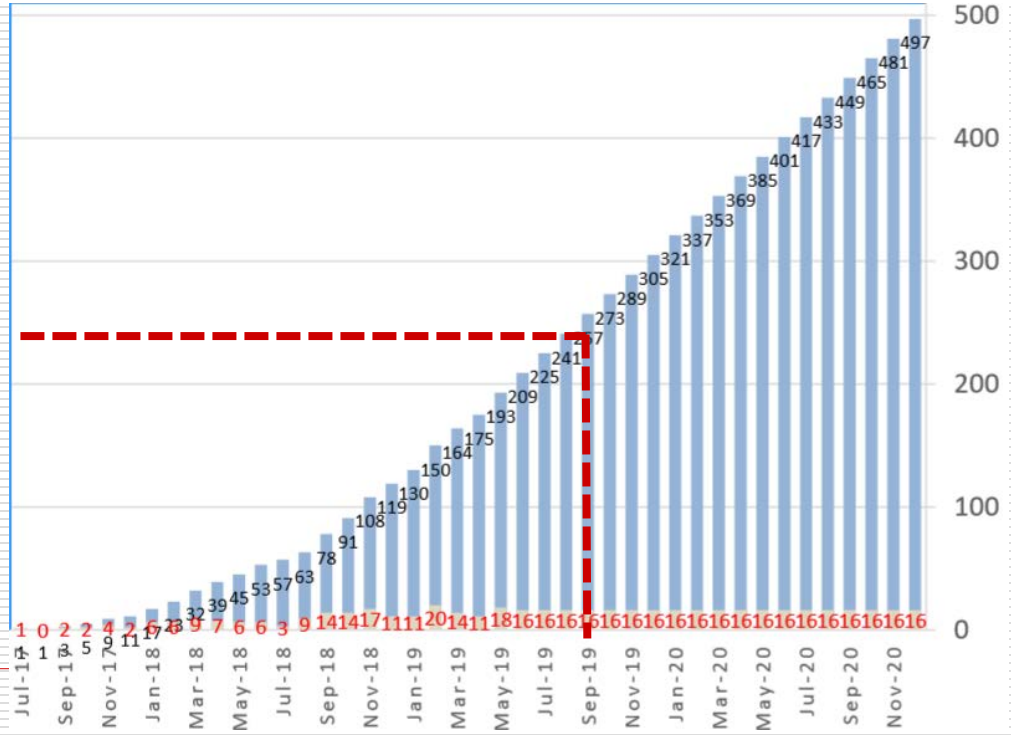
TWIST (on-going)

TWIST
Tenecteplase in Wake-up Ischaemic Stroke Trial

- **Tenecteplase** vs. open control
- **500 patients,** symptom duration **<4.5 hours since wake-up**, no advanced imaging
- **CT-angiograpy and –perfusion** strongly encouraged, but not used for patient selecton
- Patients with **large vessel occlusion** can be randomised before thrombectomy
- Outcome: **Functional outcome** at 3 months

TWIST: Status

- **234 patients**, 61 centres, 8 countries
- Target end of recruitment: **December 2020**
- New centres are welcome!



Summary - Treatment **<4.5 hours** without advanced imaging (strategy B)

- No evidence to guide practice
- TWIST will show whether treatment is beneficial within 4.5 hours of wake-up, independent of advanced imaging
- TWIST may confirm whether treatment is beneficial in patients with CT-perfusion core/penumbra mismatch

Conclusion – Thrombolytic treatment in wake-up stroke

- In patients who fulfill advanced imaging criteria, treatment should be considered

- Patients who do not fulfill these criteria, or have no access to advanced imaging, should be included into on-going trials