

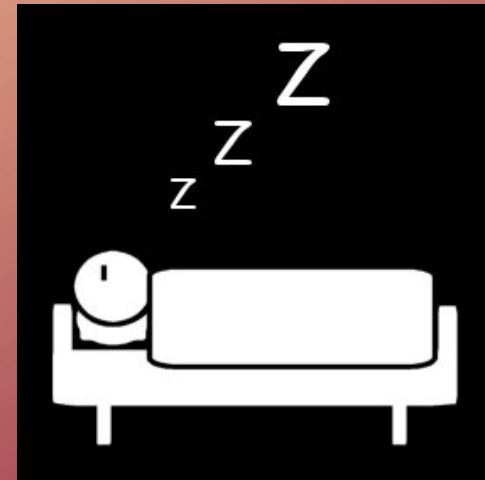


A randomised-controlled trial of tenecteplase in patients who wake up with acute ischaemic stroke

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Wake-up Stroke

- **One in five strokes occur during sleep^{1,2}**
- **Stroke onset is probably close to awakening³**



¹Mackey J, et al. *Neurology* 2011

²Moradiya et al. *J Stroke Cerebrovasc dis* 2013

³Marler JR, et al. *Stroke* 1989

Wake-up stroke

- **Patients share clinical and brain imaging findings with patients with stroke duration <4.5 hours¹⁻⁴**
- **Patients are not eligible for thrombolytic treatment, according to guidelines⁵**
- **Studies suggest that thrombolytic treatment is safe⁶**

¹Fink JN, et al. *Stroke* 2002

²Todo K et al, *Cerebrovasc Dis* 2010

³Huisa BN et al, *J Stroke Cerebrovasc Dis* 2010

⁴Silva GS, *Cerebrovasc Dis* 2010

⁵ AHA/ASA Guidelines Stroke 2018

⁶Manawadu et al, *Stroke* 2013

Study	Intervention	Patients	Radiology	Effect variable
EXTEND	Alteplase 0,9 mg/kg <i>vs.</i> placebo	(Treatment from mid-point time of wake-up to 9 hours) or treatment from 3-9 or 4.5-9 hours; core lesion < 70 ml; NIHSS score 4-26, Pre-stroke mRS score < 2	CTP penumbral mismatch or MRI DWI-FLAIR mismatch	mRS at 90 days
THAWS	Alteplase 0,6 mg/kg <i>vs.</i> control	Unknown onset (incl. onset during sleep) last known well and treatment < 4.5 hours; ASPECTS ≥ 5 ; NIHSS score ≥ 2	MRI DWI-FLAIR mismatch	mRS at 90 days
WAKE-UP	Alteplase 0,9 mg/kg <i>vs.</i> placebo	Unknown onset (incl. onset during sleep) lkw and treatment < 4.5 hours, age 18-80 years, DWI lesion < 100 ml NIHSS < 25	MRI DWI-FLAIR mismatch	mRS at 90 days
WASSABI	Alteplase 0,9 mg/kg <i>vs.</i> IAT <i>vs.</i> control	Unknown onset, last seen normal < 24 hours; NIHSS 8-22, age 18-80 years; ASPECTS ≥ 7 , mRS of < 2	CTP penumbra	mRS at 90 days
TWIST	Tenecteplase 0,25 mg/kg <i>vs.</i> control	Onset during sleep; treatment ≤ 4.5 hours since wake-up; no planned IA intervention; Limb weakness with NIHSS score > 5 and under 25 mRS score < 2	CT lesion <1/3 of MCA territory	mRS at 90 days



Rationale for a CT-based trial of tenecteplase in wake-up stroke

- Tenecteplase seems to be as effective as alteplase, and safe. Administration is easier.
- Advanced MRI imaging criteria may exclude patients from an effective treatment, and is not universally available
- We therefore want to do a pragmatic, CT-based trial of tenecteplase

Tenecteplase for acute ischaemic stroke

- Pharmacological advantages (speed of action, fibrin specificity 14x, half-life)
- Single bolus dose (no 1-hour infusion)
- Preferred treatment for acute myocardial infarction (lower risk of bleeding) ¹
- Comparable safety and efficacy to alteplase in acute ischaemic stroke

¹Van der Werf et al. ASSENT- 2 Lancet. 1999;354(9180):716-22.



Study	Intervention	Patients	Radiology	Results
ATTEST 2014	Tenecteplase 0,25 mg/kg <i>vs.</i> alteplase 0,9 mg/kg	Treatment/last known well 4 ½ hours, age over 18, NIHSS min. 1 up to 25 ASPECT Score >4 CT lesion <1/3 of MCA mRS score ≥ 2	CTA occlusion + CTP penumbra	Neurological and radiological outcomes did not differ between TNK and alteplase groups
Haley 2010	Tenecteplase 0,1 mg/kg <i>vs.</i> 0,25 mg/kg <i>vs.</i> 0,4 mg/kg <i>vs.</i> alteplase 0,9 mg/kg	Treatment 3 hours of onset. Age over 18. Large areas(greater than one lobe) of low density on CT. Measurable deficit on NIHSS(no upper limit). mRS score ≥ 2	CT	Prematurely terminated due to slow enrollment. The 0,4 mg/kg dose was discarded. No statistically persuasive differences in 90 days outcomes in the remaining groups.
Parsons 2012	Tenecteplase 0,1 mg/kg <i>vs.</i> 0,25 mg/kg <i>vs.</i> alteplase 0,9 mg/kg	Treatment 6 hours of onset. Age over 18 years. NIHSS 4 or more Excl. internal-carotid-artery & vertebrobasilar occlusion. mRS score ≥ 2	CTA occlusion + CTP penumbra (perfusion lesion 20% greater than core)	Tenecteplase associated with significantly better reperfusion and clinical outcomes than alteplase in patients selected on the basis of CT perfusion
NOR- TEST 2016	Tenecteplase 0,4 mg/kg <i>vs.</i> alteplase 0,9 mg/kg	Treatment 4 ½ hours, Age over 18. Measurable deficit on NIHSS. Excl: Large hypodense ischaemic changes Premorbid	CT (For subgroup: CTA and MRI/FLAIR- DWImismatch)	Results presented at ESOC2017 and published in The Lancet Neurology.

Aims of the trial

To answer the following questions:

1. Can tenecteplase given <4,5 hours from wake-up improve functional outcome at 3 months?
2. Can multi-modal CT identify patients who are likely to benefit (and patients who are likely to be harmed) from tenecteplase?



TWIST Study Organisation

- **Sponsor: University Hospital of North Norway**
- **Trial Co-ordinating Centre**
- **Trial Steering Committee**
 - Eivind Berge, Hanne Krarup Christensen, Gian Marco De Marchis, Bent Indredavik, Dalius Jatužis, Janika Kõrv, Erik Lundström, Ellisiv B. Mathiesen, Jesper Petersson, Jukka Putaala, Tom Robinson, Ole Morten Rønning, Arnstein Tveiten, David Werring
- **Data Monitoring Committee**
 - Terje Pedersen (Chair), Hans Wedel, Peter Sandercock



Trial Co-ordinating Centre



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London

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Marchis/Stefan Engelter

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Switzerland





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British Heart Foundation

Swiss Heart Foundation

Boehringer Ingelheim – cost of tenecteplase

Inclusion criteria

- Stroke symptoms upon awakening that were not present before sleep
- Clinical diagnosis of stroke with limb weakness (NIHSS score >5) or aphasia
- Treatment possible <4.5 hours of awakening
- Written consent according to national directives

Exclusion criteria

- Age < 18 years
- NIHSS score >25 or NIHSS consciousness score >2, or seizure during stroke onset
- CT findings:
 - Large infarction
 - ICH or structural brain lesions which can mimic stroke
- Patients where it has been decided to perform intra-arterial interventions for proximal cerebral artery occlusion
- Persistent blood pressure elevation

Exclusion criteria

- Blood glucose < 2.7 or > 20.0 mmol/L
- Contraindications to tenecteplase
- Pregnancy, child birth during last 10 days, or breastfeeding
- Other serious or life-threatening disease prior to stroke, severe mental or physical disability
- Active bleeding or high risk of bleeding

23. august 2017

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Practice Randomisation - This is not using live data

Thank you, you have just included the following patient in TWIST:

Patient number	999013
Patient initials	jj
Year of birth	1950
Sex	Female
Weight	70 kg

Full-screen Snip

The patient was allocated to "Tenecteplase"

Dose mg	17 mg
Dose ml	3,4 ml

Start of treatment

- **Give tenecteplase within 4.5 hours of wake-up, using the dose (in mg and mL) given above, and follow these instructions:**
 - Prepare the tenecteplase solution 5 mg/mL with the kit: Fill the vial (tenecteplase 10.000 U/50 mg) with 10 mL NaCl 0.9% from the pre-filled syringe).
 - Use the dosage table to select dose in mL (as above: 3,4 mL)
 - Draw the exact dose in mL back into the syringe. Important: Ignore any dose/volume guidance on the syringe (which is for myocardial infarction).
 - Inject the dose over approximately 10 seconds.
 - Flush with 20 mL NaCl 0.9% after injection.
- **Measure blood pressure at 0 minutes, 30 minutes, 1 hour, and 3 hours (all patients)**
- **Refer the patient to CT and CTA at 24±6 hours after randomisation (all patients)**
- **When treatment has been given and blood pressure at 3 hours have been measured: Fill in the form "Day 1 Treatment and monitoring".**

[Click here to fill in the form "Day 1 Treatment and monitoring"](#). (The form can also be found under the My actions/Data entry menu to the left).

24-hour help-line

Please contact us any time if you have questions: E-mail address: twist@uit.no Tel. number (24/7): +47 77627120 / 77627074.

Role of CT imaging

1. Day 1 (before randomisation):
 - CT
 - CT-A (if possible)
 - (CT-P, - in centres participating in CT-P substudy)
2. Day 2:
 - CT
 - CT-A (in patients with occlusion on Day 1)



eCRF and Brain Scans

- Day 1 Treatment and monitoring
- Day 2 Monitoring and imaging
- Day 7 Discharge
- Day 90 Centralised Follow-up
- Collection of Brain Scans and Scan Transfer form



Follow-up after 3 months

- Centralized, nationwide
- Telephone interview (or postal letter)

Economical compensation

- Compensation for work
NOK 3000 (appr. 300 €) pr patient
enrolled in the study
- Cost of tenecteplase

Time schedule

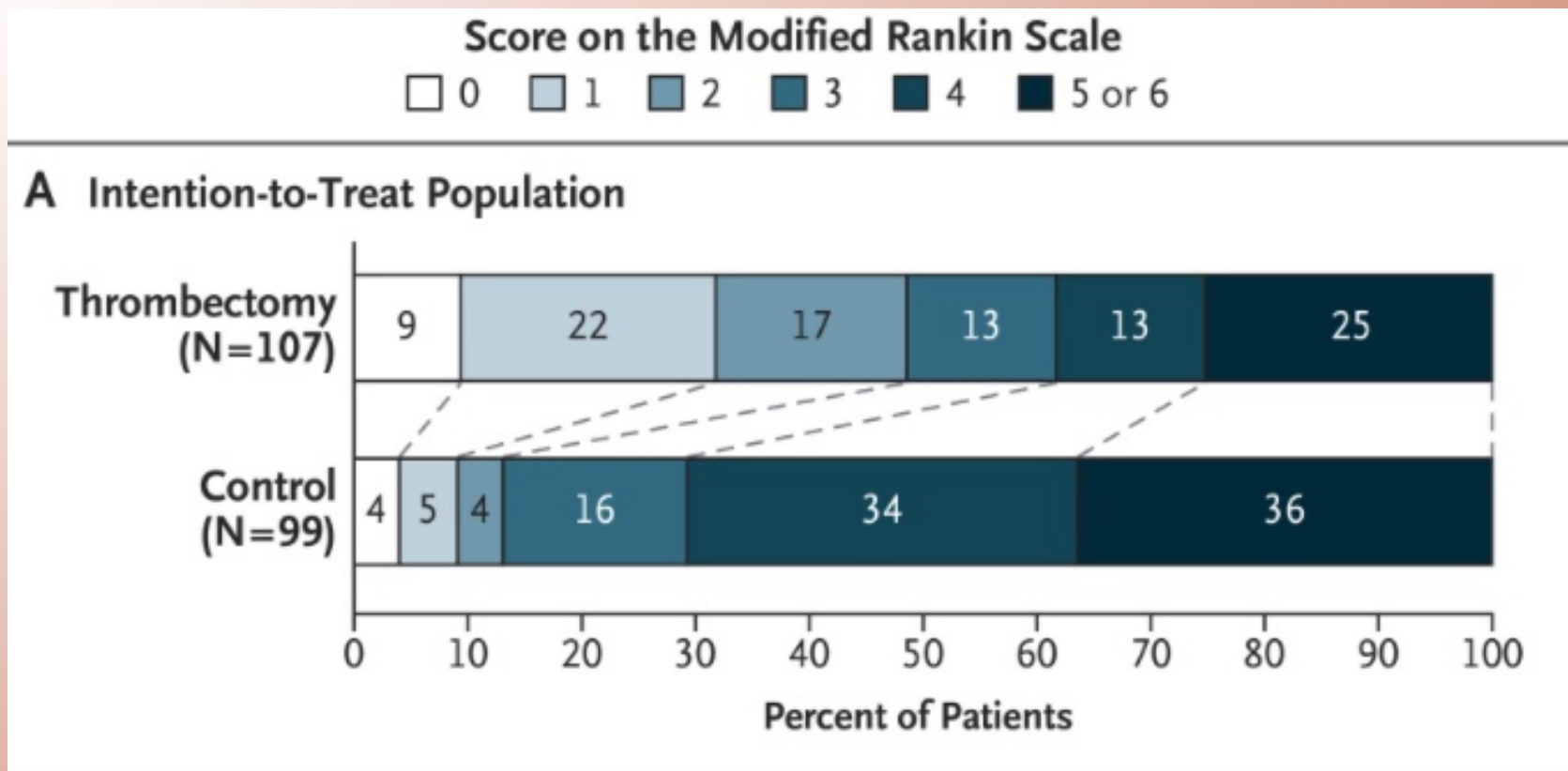
- **2017 June:** Start of patient inclusion
- **2017, August:** Start-up meeting for all Nordic countries at Nordic Stroke Congress in Aarhus
- **2017, Autumn/Winter:** Skype Initiation Meetings
- **2018, Spring:** National meetings; Switzerland/January, Sweden/February, Denmark/March, Lithuania/April, ESOC Lunch Gothenburg May
- **2019, December:** End of follow-up
- **2020, May:** Presentation at ESOC 2020

If patients with wake-up stroke may benefit from thrombolytic treatment up to 4.5 hours after awakening, and these patients can be shown to benefit from treatment, this will substantially increase the proportion of patients who can be treated!



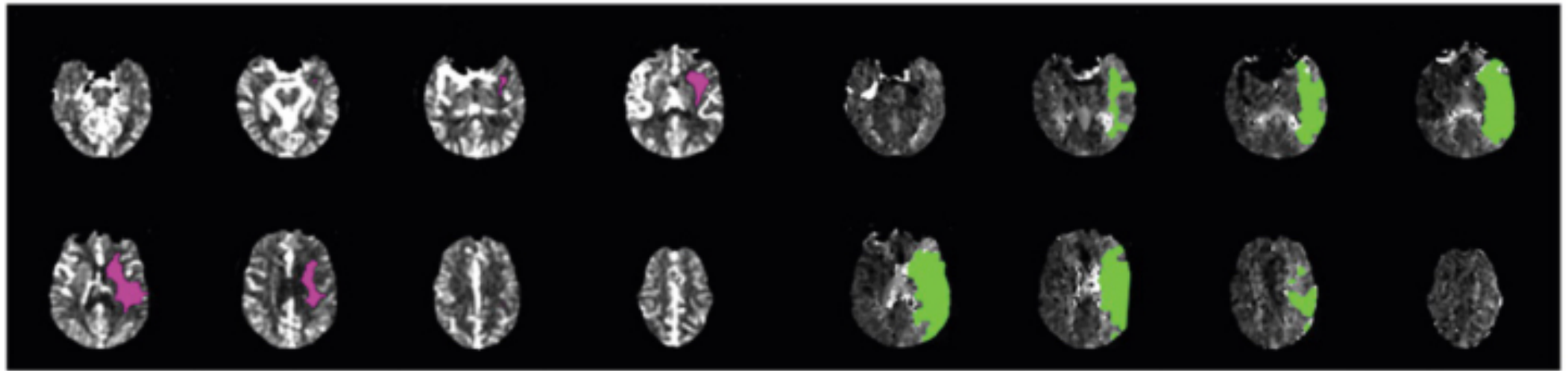
DAWN Trial

- Thrombectomy for stroke 6-24 hours
- n = 206
- NIHSS 10
- 60% wake-up stroke
- Small infarct core and clinical/infarct deficit
- Outcome (mRs 0-2, 90 days were 48% vs 13%)



Defuse 3

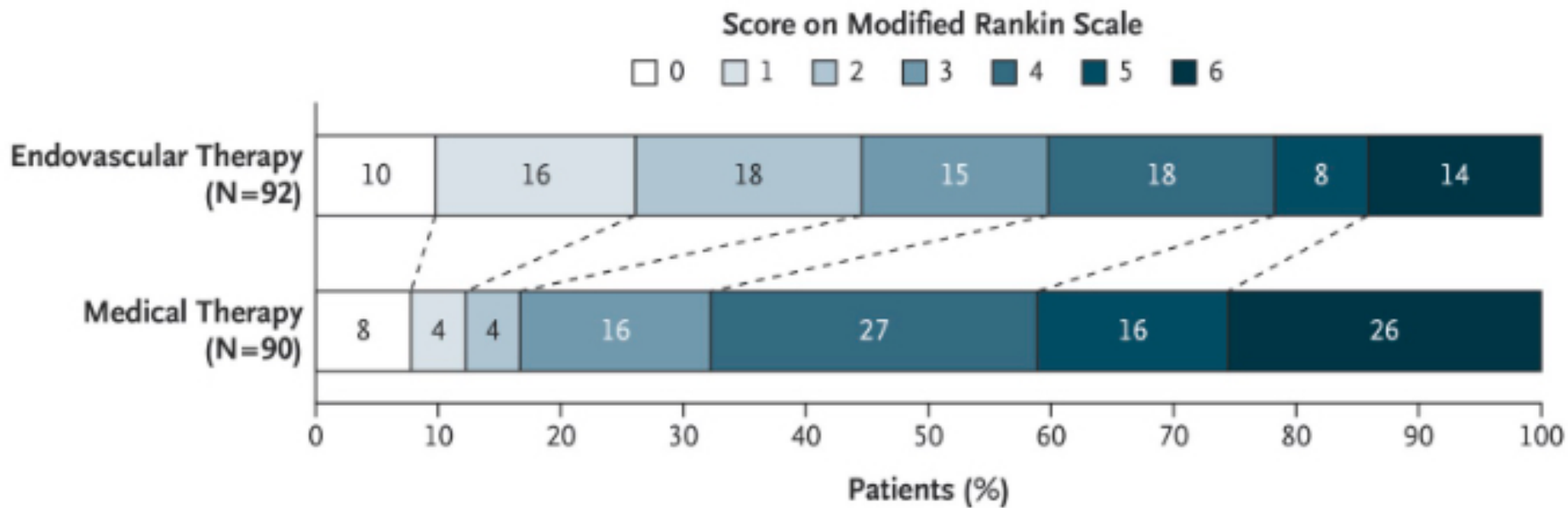
- Thrombectomy for stroke 6-16 hours (lkw)
- n = 183
- NIHSS ≥ 6
- Radiological Mismatch = Initial infarct size of less than 70 ml and mismatch ratio over 1.8
- Primary outcome mRs 0-2 (44% vs 16%)



Volume of Ischemic Core, 23 ml

Volume of Perfusion Lesion, 128 ml

Mismatch volume, 105 ml
Mismatch ratio, 5.6



Tromsø

