Is it time to WAKE-UP? EXTENDING the tPA window for acute ischemic stroke

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Disclosures
● No financial conflicts of interest to disclose

Objectives
1. Identify appropriate therapy for patients who present with acute ischemic stroke
2. Assess if current literature supports extension of tPAs for patients with unknown symptom onset
3. Apply new findings to clinical scenarios

Abbreviations
● AIS = acute ischemic stroke
● ASPECTS = Alberta Stroke Program Early CT Score
● DW-MRI = diffusion-weighted magnetic resonance imaging
● FLAIR = fluid attenuated inversion recovery
● ICA = internal carotid artery
● ICH = intracerebral hemorrhage
● LVO = large vessel occlusion
● LKW = last known well
● MCA = middle cerebral artery
● mRS = modified Rankin Scale
● NIHSS = National Institutes of Health Stroke Scale
● OHS = Oxford Handicap Score
● sICH = symptomatic intracerebral hemorrhage
● tPA = tissue plasminogen activator
● WUS = wake-up stroke

Patient Case - P.C.
● 65 year-old male presented to ED with L side weakness, slurred speech
  ○ Last seen well 8h ago per wife
  ○ NIHSS 12, mRS 1, ASPECTS 8
● PMH: DM, HLD, CAD
● Home meds: ASA, metformin, atorvastatin, metoprolol
● Vitals: BP 165/95
● Labs: sr/l
● CT head: L MCA infarct with no cerebral hemorrhage or edema
● DWI: hyperintense area in L MCA
● FLAIR: no abnormalities

How should P.C. be managed?
  a. Administer tPA - 0.9 mg/kg, 10% IV bolus over 1 minute and the remainder infused over 60 minutes
  b. Administer aspirin 325 mg and admit to stroke or intensive care unit
  c. Send patient for immediate thrombectomy
Initial Evaluation of Acute Ischemic Stroke

- History of symptom onset
- Neurological and physical examination
- Imaging
  - CT or MRI of the head
- Assessment of stroke severity with NIHSS and mRs
- Assess tPA eligibility - “Door-to-needle within 60 minutes”
- Assess mechanical thrombectomy eligibility

Modified Rankin Scale and NIHSS

**mRs**
- Measures degree of disability or dependence in ADLs of people who undergo neurological disability
- Assesses baseline activity with a scale of: 0-6 via a patient questionnaire
  - 0 = no disability
  - 6 = death
  - 0-2 = favorable outcome

**NIHSS**
- Quick diagnostic tool to assess stroke severity, determine treatment, and predict patient outcomes
- 11 item scale that assesses cognitive function, consciousness, communication, and motor function
- Each item scores 0-4 (no impairment to complete)
  - 0-4 minor, 5-15 moderate, 16-20 severe, >20 severe

DWI and FLAIR Imaging

**DWI**
- Sensitive in detection of small and early infarcts
- Shows high signal intensity within the first few minutes after ischemic stroke, up to 4.5 hours

**FLAIR Imaging**
- Inverse recovery sequence with long inversion time
- Findings are positive 6-12 hours after onset of symptoms

ASPECTS

- 10-point quantitative score used to assess early ischemic changes on non-contrast head CT
- Mainly Segmental assessment of the MCA, but other areas included
- Used to assess thrombectomy eligibility
- Default 10 points, 1 point deducted per region of MCA involved
  - $\geq 7$ = worse functional outcome at 3 months

Acute Ischemic Stroke Treatment Guidelines

Extending tPA for acute ischemic stroke
Thrombectomy Guideline Recommendations

- "Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria..." (Strong recommendation, high-quality evidence)
- "In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended." (Strong recommendation, high-quality evidence)
- "In selected patients with AIS within 16 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable." (Moderate recommendation, moderate-quality evidence)

Thrombectomy Inclusion Criteria

Within 6 hours of symptom onset:
- Age ≥18
- Pre-stroke mRs 0-2, NIHSS ≥6, and ASPECTS ≥6
- Causative occlusion of ICA or MCA
- Treatment can be initiated (groin puncture) within 6 hours of onset

Thrombectomy Inclusion Criteria

DEFUSE: 6 to 16 hours after last known normal
- Age 18-85
- Pre-stroke mRs 0-2, NIHSS >6, and ASPECTS >6
- M1 MCA or ICA occlusion and perfusion mismatch on CT perfusion or MRA (RAPID software)
  - Initial infarct <70 mL, ischemic tissue-initial infarct volume >1.8, and absolute volume potentially reversible ischemia >15 mL
- Treatment can be initiated (groin puncture) between 6-16 hours of last known well

Thrombectomy Inclusion Criteria

DAWN: 6 to 24 hours after last known normal
- Age >18
- Pre-stroke mRs 0-1, NIHSS ≥10 if ≥80 y/o, ≥20 otherwise, and ASPECTS ≥6
- M1 MCA or ICA occlusion, ≤1/3 MCA territory involvement, and perfusion mismatch on DWI
  - 0-20 mL infarct size for ≥80; 0-30 mL for <80, 31-50 for NIHSS ≥20 and ≤80
- Treatment can be initiated (groin puncture) between 6-24 hours of last known well

tPA Guideline Recommendations

- "IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 15% of dose given as bolus over 1 minute) is recommended for selected patients who may be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state." (Strong recommendation, high-quality evidence)
- "IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 15% of dose given as bolus over 1 minute) is also recommended for selected patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well" (Strong recommendation, moderate-quality evidence)

tPA Inclusion Criteria

Within 3 hours of symptom onset:
- Age ≥18
- Clinical diagnosis of stroke with clinically meaningful neurologic deficit
- Baseline CT with no evidence of intracranial hemorrhage
- No active anticoagulation
- No history of diabetes and prior ischemic stroke

3 to 4.5 hours of symptom onset:
- Age ≤80
- NIHSS ≤25
- No active anticoagulation
- No history of diabetes and prior ischemic stroke
tPA Exclusion Criteria

Exclusion Criteria

- CT signs of ICH, multilobar infarction, or SAH
- Active internal bleeding
- History of ICH
- Stroke or serious head injury within 3 months
- Concurrent use of DTI or Xa inhibitors with elevated sensitive lab tests
- SBP >185 or DBP >110 mmHg
- Anticoagulation with INR >1.7
- Heparin administered within last 48 hours resulting in elevated aPTT
- Glucose <50 or >400 mg/dL
- Symptoms of SAH
- PT <100,000/mm3

Relative Exclusion Criteria

- Minor or rapidly improving stroke symptoms
- Pregnancy
- Seizure at onset with postictal residual neurologic impairments
- Major surgery or serious trauma within past 2 weeks
- GI or urinary tract hemorrhage within past 3 weeks

Summary of Recommendation Literature

<table>
<thead>
<tr>
<th>Trial</th>
<th>Time</th>
<th>Primary Benefit</th>
<th>Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS-II</td>
<td>&lt;3 hours</td>
<td>90-day mRs 0-1: 13% absolute</td>
<td>36-hour ICH: 5.8% absolute</td>
</tr>
<tr>
<td>(N=333) 1995</td>
<td></td>
<td>benefit, OR 1.7 (1.1-2.6)</td>
<td>increase</td>
</tr>
<tr>
<td></td>
<td>3-4.5 hours</td>
<td>90-day mRs 0-2: 7% absolute</td>
<td>Any ICH: 3.4% absolute</td>
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<tr>
<td>ECASS-II</td>
<td>2008</td>
<td>benefit, OR 1.34 (1.02-1.76)</td>
<td>increase, OR 1.73 (1.24-</td>
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<tr>
<td>(N=821)</td>
<td></td>
<td>NNT 15</td>
<td>2.42)</td>
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<td>NNT 15</td>
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<td>NHN 10</td>
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<td>NNH 17</td>
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<td>NHN 10</td>
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<td></td>
<td></td>
<td></td>
<td>NNH 10</td>
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Other Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Time</th>
<th>Primary Benefit</th>
<th>Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIAS-2</td>
<td>3-9 hours</td>
<td>Alive and independent per OHS</td>
<td>No significant difference in AE</td>
</tr>
<tr>
<td>(N=153) 2009</td>
<td></td>
<td>0-2 at 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not significant</td>
<td></td>
</tr>
<tr>
<td>IST-3</td>
<td>&lt;6 hours</td>
<td>90-day good clinical outcome</td>
<td>No significant difference in sICH and</td>
</tr>
<tr>
<td>(N=3035) 2012</td>
<td></td>
<td>Not significant</td>
<td>90-day mortality</td>
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Wake-up Stroke

- Situation where patient awakens with stroke symptoms not present prior to falling asleep
- 1 in 5 ischemic stroke patients present with WUS
- Excluded from most ischemic stroke trials, thus not eligible for reperfusion therapy
- DWI and FLAIR mismatch aids in estimating time of stroke onset in this population
- Studies now including WUS patients

Literature Evaluation

Extending tPA for acute ischemic stroke
MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset.

**WAKE-UP Trial**

**Objective**
- To determine effect of tPA on functional outcomes in patients with an unknown time of stroke onset and a mismatch between diffusion-weighted imaging and FLAIR findings on MRI

**Design**
- Randomized, double blind, parallel assignment, placebo-controlled, multicenter trial

**Inclusion**
- Age 18-80 with clinical signs of acute stroke, able to complete ADLs prior to stroke, last known well time >4.5h prior to presentation, abnormal signal on DWI, negative FLAIR imaging

**Exclusion**
- Hemorrhage on MRI, lesion larger than ⅓ the territory of MCA, planned thrombectomy, NIHSS >25, contraindication to alteplase (except onset >4.5h)

**WAKE-UP Trial - Intervention**
- IV alteplase 0.9 mg/kg (max 90 mg), 10% over 1 minute followed by 60 minute infusion or placebo; stratified by age (<60 or >60) and NIHSS (<10 or >10)

**Outcomes**
- Primary
  - 90-day mRS 0-1
- Secondary
  - Ordinal score on mRS at 90 days
  - 90-day mRS 0 for NIHSS <7; mRS 0-1 for NIHSS 8-14; mRS 0-2 for NIHSS >14
  - 90-day global outcome on 5 scales: mRS and NIHSS 0-1, Barthel Index 85-100, Glasgow Outcome Scale 5
- Safety
  - Death or mRS 4-6 at 90 days
  - Symptomatic ICH causing deterioration in neurologic symptoms
  - Incidence of parenchymal hematoma on MRI 22 to 36 hours after randomization

**WAKE-UP Trial - Results**

**Sample**
- N = 503, tPA = 254, placebo = 249
  - Trial stopped early before reaching anticipated 800 patients due to lack of funding

**WAKE-UP Trial - Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alteplase (N=254)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median NIHSS score (IQR)</td>
<td>6 (4-9)</td>
<td>6 (4-9)</td>
</tr>
<tr>
<td>Reason for unknown time of symptoms onset - No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime sleep</td>
<td>227 (89.4)</td>
<td>222 (89.2)</td>
</tr>
<tr>
<td>Daytime sleep</td>
<td>12 (4.7)</td>
<td>11 (4.4)</td>
</tr>
<tr>
<td>Aphasia, confusion, or other</td>
<td>15 (5.9)</td>
<td>16 (6.6)</td>
</tr>
<tr>
<td>Median time from symptom recognition to treatment (IQR) - hr</td>
<td>3.1 (2.8–3.8)</td>
<td>3.2 (3.8–3.9)</td>
</tr>
<tr>
<td>Interval between last known well and treatment (IQR) - hr</td>
<td>10.3 (8.1–12.0)</td>
<td>10.4 (8.1–12.1)</td>
</tr>
<tr>
<td>Intracranial ICA occlusion - No/total (%)</td>
<td>24/248 (9.6)</td>
<td>110/464 (4.5)</td>
</tr>
</tbody>
</table>

**WAKE-UP Trial - Primary Outcome**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alteplase (N=254)</th>
<th>Placebo (N=249)</th>
<th>Adjusted Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome at 90 days</td>
<td>131 (51.3)</td>
<td>112 (45.8)</td>
<td>1.61 (1.09-2.38)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Safety**
- Death or mRS 4-6 at 90 days
- Symptomatic ICH causing deterioration in neurologic symptoms
- Incidence of parenchymal hematoma on MRI 22 to 36 hours after randomization
### WAKE-UP Trial - Safety

#### Primary Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alteplase (n=251)</th>
<th>Placebo (n=244)</th>
<th>Adjusted Value OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or dependency at 90 days</td>
<td>33 (13.5)</td>
<td>44 (18.3)</td>
<td>0.68 (0.39–1.18)</td>
<td>0.17</td>
</tr>
<tr>
<td>Death at 90 days</td>
<td>10 (4.1)</td>
<td>3 (1.2)</td>
<td>3.38 (0.92–12.52)</td>
<td>0.07</td>
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</table>

#### Secondary Outcome

<table>
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<tr>
<th>Outcome</th>
<th>Alteplase (n=254)</th>
<th>Placebo (n=249)</th>
<th>Adjusted Value OR, (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal hemorrhage type 2</td>
<td>10 (4.0)</td>
<td>1 (0.4)</td>
<td>10.46 (1.32–82.77)</td>
<td>0.03</td>
</tr>
<tr>
<td>Symptomatic ICH by Definition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SITS-MOST</td>
<td>5 (2.0)</td>
<td>1 (0.4)</td>
<td>4.66 (0.77–42.87)</td>
<td>0.15</td>
</tr>
<tr>
<td>ECASS II</td>
<td>7 (2.8)</td>
<td>3 (1.2)</td>
<td>2.40 (0.60–9.52)</td>
<td>0.21</td>
</tr>
<tr>
<td>ECASS III</td>
<td>6 (2.4)</td>
<td>1 (0.4)</td>
<td>6.04 (0.73–50.87)</td>
<td>0.10</td>
</tr>
<tr>
<td>NINDS</td>
<td>20 (8.0)</td>
<td>12 (4.8)</td>
<td>1.78 (0.84–3.71)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

### WAKE-UP Trial

**Strengths**
- Multicenter, randomized, double-blind, RCT
- First study which uses perfusion vs time to tPA

**Weaknesses**
- Trial stopped early due to funding, did not meet 370 patients per group for adequate power
- More patients in tPA group had intracranial occlusion of internal carotid artery
- 20% of patients with large occlusion would have qualified for treatment with thrombectomy
- Generalizability: special training with software-based imaging

### WAKE-UP Trial - Author's Conclusions

- In patients with acute stroke with an unknown time of onset, intravenous alteplase guided by a mismatch between diffusion-weighted imaging and FLAIR in the region of ischemia resulted in a significantly better functional outcome and numerically more intracranial hematomas than placebo at 90 days

### WAKE-UP Trial - Presenter's Conclusions

- Generalizability: Over 5 year period, 1362 patients screened to obtain 500 that met randomization criteria
- Only select group of patients
- Most patients with NIHSS scores <10
- Benefit of tPA found in this trial may be due to chance; non-significant harm due to underpowered study

### 2019 Acute Ischemic Stroke Update - New Recommendation

- Extending tPA for acute ischemic stroke
tPA Time Window Recommendation

- 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 recognition can be beneficial 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 a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR. (Moderate recommendation, moderate quality evidence)

Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke.

EXTEND Trial

Objective
- To determine if tPA given between 4.5-9 hours after stroke onset or WUS would benefit patients who had small core volume of cerebral infarction that was disproportionate to a larger area of hypoperfusion

Design
- Phase III, multicenter, randomized, double blind, placebo-controlled trial

Inclusion
- ≥18 years old, mRs <2 before enrollment, 4.5-9 hours stroke onset with NIHSS ≥4-26, had hypoperfused but salvageable regions of brain detected on automated imaging (RAPID)

Exclusion
- ICH via imaging, rapidly improving symptoms (NIHSS <4), pre-stroke mRs ≥2, eligible for endovascular clot retrieval, ischemic core >1/3 MCA territory, pregnant, life expectancy <1 year

EXTEND Trial - Intervention
- IV alteplase 0.9 mg/kg (max 90 mg), 10% over 1 minute followed by 60 minute infusion or placebo; stratified by time of intervention (>4.5-6 hours and >6-9 hours)

Outcomes
- Primary
  - 90-day mRs 0-1
- Secondary
  - 90-day improvement of ≥1 on mRs
  - 90-day mRs 0-2
  - Percent reperfusion at 24 hrs ≥90%
- Safety
  - Death within 90 days
  - Symptomatic ICH within 36 hours after intervention with >4 point increase in NIHSS from baseline

EXTEND Trial - Results

Sample
- N = 225, tPA = 113, placebo = 112
  - Trial stopped early before reaching anticipated 310 patients
  - Needed 310 for 80% power to detect 15% difference between treatment and placebo group

EXTEND Trial - Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alteplase (N=113)</th>
<th>Placebo (N=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median NIHSS Score (IQR)</td>
<td>12.0 (8.0–17.0)</td>
<td>10.0 (6.0–16.0)</td>
</tr>
<tr>
<td>Median time from stroke onset to randomization - No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4.5 to 6 hours</td>
<td>12 (10.8)</td>
<td>11 (9.8)</td>
</tr>
<tr>
<td>&gt;6 to 9 hours</td>
<td>28 (24.4)</td>
<td>28 (25.0)</td>
</tr>
<tr>
<td>Awake at time of stroke</td>
<td>73 (64.6)</td>
<td>73 (65.2)</td>
</tr>
<tr>
<td>Median time from stroke onset to hospital arrival (IQR) - min</td>
<td>308 (227–362)</td>
<td>289 (240–357)</td>
</tr>
<tr>
<td>Median time from stroke onset to IV therapy (IQR) - min</td>
<td>452 (374–648)</td>
<td>456 (376–530)</td>
</tr>
<tr>
<td>Median time from hospital arrival to IV therapy (IQR) - min</td>
<td>124 (81–176)</td>
<td>127 (87–174)</td>
</tr>
</tbody>
</table>
EXTEND Trial - Primary

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alteplase (n=113)</th>
<th>Placebo (n=112)</th>
<th>Adjusted Effect Size (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score of 0 to 1 on mRs</td>
<td>43/113 (37.4)</td>
<td>33/112 (29.5)</td>
<td>1.44 (1.01–2.06)</td>
<td>0.04 NNT 17</td>
</tr>
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</table>

EXTEND Trial - Safety

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alteplase (n=113)</th>
<th>Placebo (n=112)</th>
<th>Adjusted Effect Size (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death within 90 days after intervention</td>
<td>13 (11.5)</td>
<td>10 (8.9)</td>
<td>1.17 (0.57–2.40)</td>
<td>0.67</td>
</tr>
<tr>
<td>Symptomatic ICH within 36 hr after intervention</td>
<td>7 (6.2)</td>
<td>1 (0.9)</td>
<td>7.22 (0.97–53.54)</td>
<td>0.053</td>
</tr>
</tbody>
</table>

EXTEND Trial - Author's Conclusions

- Ischemic stroke patients with salvageable brain tissue presenting 4.5–9 hours from onset or with WUS who received alteplase achieved better functional outcomes, reperfusion and early neurological improvement. Mortality was comparable despite numerically more sICH

EXTEND Trial - Presenter's Conclusions

- Generalizability: use of special imaging software to detect penumbral mismatches on imaging limits application to majority of hospitals
- Early discontinuation of the study may have lead to overestimation of benefit
- Power not met: significant difference in the benefit of tPA administration, non-significant harm

Bottom Line

- Both of these studies are examples of trials stopped early that likely suffer from overestimation of benefit
- New imaging modalities for unknown AIS onset shifts away from a time to tPA administration to a perfusion-based strategy for salvageable tissue
- Unknown benefit in patients with strokes with unknown onset of symptoms, but tPA use in these patients trends toward increased early mortality and increased sICH
- Further studies with enough power to detect significant differences in efficacy and safety needed to change current practice
Patient Case - P.C.

- 65 year-old male presented to ED with L side weakness, slurred speech
  - Last seen well 8h ago per wife
  - NIHSS 12, mRs 1, ASPECTS 8
- PMH: DM, HLD, CAD
- PM: ASA, metformin, atorvastatin, metoprolol
- Vitals: BP 165/95
- Labs: nil
- CT head: L MCA infarct with no cerebral hemorrhage or edema
- DWI: hyperintense area in L MCA
- FLAIR: no abnormalities

How should P.C. be managed?
- a. Start tPA administration - 0.9 mg/kg, 10% IV bolus over 1 minute and the remainder infused over 60 minutes
- b. Administer aspirin 325 mg and admit to stroke or intensive care unit
- c. Send patient for immediate thrombectomy

Future Studies

**TIMELESS Trial: Tenecteplase in Stroke Patients Between 4 and 24 Hours**
(NCT03785678)
- Safety and efficacy of tenecteplase 0.25 mg/kg (max 25 mg) single bolus vs placebo in AIS in patients with perfusion mismatch
- 90-day mRs; 90-day functional independence, 24h reperfusion, additional stroke scale outcomes
- Currently recruiting; estimated completion September 30, 2020

**TWIST Trial: Tenecteplase in Wake-up Ischaemic Stroke Trial**
(NCT03181360)
- Assessing if tenecteplase given within 4.5h of awakening improves functional outcomes at 3 months vs placebo
- 3-month mRs score improvement, 7-day sICH, asymptomatic ICH, recurrent ischemic stroke, and all-cause mortality
- Currently recruiting; estimated completion December 31, 2022

Acknowledgements

- Bryson Duhon, PharmD, BCPS
- Justin Gonzalez, PharmD, BCPS
- Y-Nha Nguyen, PharmD, BCPS, BCCCP, BCCP

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