At the end of this session, the learner will be able to:
1. Define wake up stroke
2. Describe current treatment for wake up strokes
3. Evaluate current literature regarding wake up stroke treatment options
I Woke Up Like This:
Intravenous tPA in Wake Up Strokes

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November 1, 2016 at 3:00 and November 4, 2016 at 3:00
UHS and McDermott Building

Learning Objectives:
At the completion of this activity, the participant will be able to:

1. Define wake up strokes
2. Describe current treatment for wake up strokes
3. Evaluate current literature regarding wake up stroke treatment options

Assessment Questions:

T  F  Wake up strokes are classified as ischemic strokes only.
T  F  Current guidelines recommend the use of tPA for treatment of wake up strokes.
T  F  Current literature supports the use of tPA in certain patients with wake up strokes.

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Speaker Disclosure: Kyllie Shae Ryan-Hummel has indicated she has no relevant financial relationships to disclose relative to the content of her presentation.
I. Introduction

a. Stroke defined

i. Stroke, also known as a cerebrovascular accident (CVA), is sudden neurological dysfunction resulting from an abrupt decrease in blood perfusion to the brain that results in tissue hypoxia.

ii. Classified into two broad categories

1. Ischemic
2. Hemorrhagic

iii. Oxygen deprivation

1. Hypoxia → global state of oxygen deprivation
2. Ischemia → oxygen deprivation to specific tissues → damage is potentially reversible
3. Infarction → oxygen deprivation to specific tissues → tissue death

b. Epidemiology

i. 795,000 people in the United States (US) have a stroke annually

1. 610,000 are first time strokes
2. 185,000 are recurrent strokes

ii. Approximately 6.6 million American adults (over 20 years of age) have had a stroke

iii. Morbidity and mortality

1. Stroke accounts for nearly 130,000 deaths each year
2. Currently the 5th leading cause of death in Americans

   a. African Americans disproportionately affected

      i. 3rd leading cause of death in African Americans
      ii. African Americans are twice as likely than Caucasians to have a stroke

b. In 2013, age-adjusted death rates for strokes were

   i. African Americans 65.7 per 100,000
   ii. Caucasians 46.9 per 100,000
   iii. Asians 39.6 per 100,000

   c. Uneven distribution across the United States

      i. Stroke belt

         1. Southern US with a 20% higher stroke mortality compared to the rest of the nation
         2. Comprised of 11 states: Alabama, Arkansas, Georgia, Indiana, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, and Virginia

      ii. Stroke belt buckle

         1. Area with a 40% higher stroke mortality compared to the rest of the nation
         2. Within the stroke belt, comprised of North Carolina, South Carolina, Georgia

II. Etiology and pathophysiology

a. Background

i. Estimated 87% of all strokes are ischemic in nature

ii. The remaining 13% of all strokes are hemorrhagic in nature

   1. 10% intracerebral hemorrhages (ICH)
   2. 3% subarachnoid hemorrhages (SAH)
b. Etiologies of ischemic stroke\textsuperscript{7,8}
   i. Large artery atherosclerosis
   ii. Lacunar infarct/small-vessel infarct
   iii. Cardioembolism
   iv. Other etiology (systemic hypoperfusion)
   v. Cryptogenic or undetermined etiology
c. Hemorrhagic transformation\textsuperscript{9}
   i. Bleeding that occurs after an initial ischemic event
   ii. Can occur whether or not any stroke treatment occurred
d. Modifiable and non-modifiable risk factors\textsuperscript{6}

<table>
<thead>
<tr>
<th>Table 1. Stroke Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modifiable</strong></td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td><strong>Cardiovascular disease</strong></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
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<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Infective endocarditis</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Alcohol intake</td>
</tr>
<tr>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td><strong>Estrogen use</strong></td>
</tr>
<tr>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
</tr>
</tbody>
</table>

III. Signs and symptoms of stroke can include\textsuperscript{10}
   a. Loss of sensation or ability to move
   b. Facial droop
   c. Unilateral weakness
   d. Ataxia
   e. Diplopia
   f. Dysarthria
   g. Vertigo

IV. Public awareness \rightarrow FAST acronym\textsuperscript{11}
   a. Important aid to help recognize the signs of a stroke
      i. Time is brain
      ii. Faster treatment \rightarrow better outcomes
   b. Based on the Cincinnati Prehospital Stroke Scale (CPSS)
      i. Quick assessment used to identify presence of stroke
         1. Elements tested
            a. Facial droop
            b. Arm drift
            c. Speech
         2. At least one CPSS element is seen in 88% of all strokes and transient ischemic attacks

Long Term Complications Associated with Ischemic Strokes\textsuperscript{6,12-20}

I. Long-term outcomes\textsuperscript{6,12-14}
   a. Number one leading cause of preventable disability in the United States\textsuperscript{6,14,15}
      i. Costs $34 billion annually
      ii. Visual impairment persists in 21% of stroke patients
      iii. Women have greater disability compared to male counterparts
      iv. Status of Medicare patients with a hospital discharge diagnosis of stroke
         1. 24% went to inpatient rehabilitation centers
         2. 31% went to skilled nursing facilities
         3. 45% returned directly home
            a. 32% of these had home health services

Figure 2. FAST Acronym
   - Face: Facial droop or asymmetry
   - Arm: Sudden weakness or tingling
   - Speech: Slurred speech
   - Time: Time is brain

b. 13% were not discharged with alternate sources of care

b. Outcomes
   i. Persistent neurological deficits at 6-months post-stroke
      1. 56% had no or minimal deficits
      2. 44% had moderate to severe deficits
         a. Hemiparesis
         b. Cognitive decline
   ii. Disposition to a nursing home at 6-months post-stroke
      1. 35% women
      2. 14% men

c. Stroke mortality
   i. Type of stroke
      1. Ischemic stroke incidence 57.4%
      2. Hemorrhagic stroke incidence 67.9%
   ii. Cumulative all-cause mortality
      1. At 30 days 10.5%
      2. At 1 year 21.2%
      3. At 5 years 39.8%

II. Modified Rankin Scale (mRS) is a measurement of functional outcome after a stroke (Appendix A)
   a. Favorable outcome (mRS 0-1)
   b. Unfavorable outcome (mRS 2-6)

III. Patients attaining “good” outcomes (mRS 0-1)19,20
   a. rtPA treatment within 3 hours → rtPA (33%) versus control (23%) [OR 1.75, 95% CI 1.35-2.27]
   b. rtPA treatment between 3 – 4.5 hours → rtPA (35%) versus control (30%) [OR 1.26, 95% CI 1.05-1.51]
   c. rtPA treatment greater than 4.5 hours → rtPA (33%) versus control (31%) [OR 1.15, 95% CI 0.95-1.40]

Diagnosis21-28

I. Clinical suspicion is the first step to diagnosing a stroke

II. Neuroimaging21-23
   a. Plays an essential role in the initial work-up of a suspected stroke
   b. Differentiates between ischemic and hemorrhagic strokes
      i. The goal is to identify patients who are eligible to receive intravenous or intraarterial treatment
      ii. Imaging techniques
         Figure 3. Imaging Techniques
         NECT  DWI  FLAIR

iii. Computed tomography (CT) is used as the initial imaging modality; it measures differences in tissue densities
   1. Nonenhanced CT (NECT)
      a. Most widely available imaging technique
      b. Used to rule out the presence of ICH
      c. Interpretation of NECT should be made within 45 minutes of arrival to the ED
      d. Hypodensity on NECT indicates ischemic injury
         i. Identifying the location of the infarct and extent of injury has prognostic significance and helps the practitioner determine treatment options
         ii. One of the primary diagnostic goals is to determine extent of Middle Cerebral Artery (MCA) territory involved
1. MCA territory is the area of brain that is supplied by the MCA
2. Represents about 300 mL of brain tissue
3. >1/3 MCA territory involvement represents a “critical size” in which reperfusion therapy has been associated with higher rates of symptomatic intracerebral hemorrhage (sICH) and less benefit from rtPA24

e. Grading the extent of damage24,25
   i. Alberta Stroke Program Early Computed Tomography Scores (ASPECTS)
      1. Systematic approach to assess early ischemic changes on NECT
         a. Parenchymal hypoattenuation is indicative of early ischemic changes
         b. Scored on a scale of 0-10
            i. Normal perfusion → 10
            ii. Entire MCA territory infarction → 0
         c. ASPECTS >7 are associated with decreased mortality
      2. Divides the MCA territory into 10 portions, weighted on their importance
         a. One point is deducted from an initial score of 10 for each region involved

   Figure 4. ASPECTS Grading
   http://radiologykey.com/acute-stroke-imaging/

2. CT perfusion (CTP)
   a. Used to rule out the presence of intracranial hemorrhage
   b. Identify perfusion mismatch
   c. Infarct core and penumbra ratio can identify rtPA candidates beyond the normal treatment window
      i. Infarct core → tissue that is no longer salvageable
      ii. Penumbra → tissue surrounding the infarct core
         1. Tissue is non-functioning but remains potentially salvageable if blood flow is restored
         2. Reperfusion of affected tissues greater than the critical size has not been associated with better outcomes

iv. Magnetic resonance imaging (MRI)21,22
   1. Nonenhanced
      a. Used to rule out the presence of intracranial hemorrhage
      b. Shows hyperintensity when ischemia is present
      c. Imaging technique takes longer to perform than CT
   2. Diffusion-weighted imaging (DWI)- fluid attenuated inversion recovery (FLAIR) mismatch26,27
      a. The most sensitive way to detect an acute infarction
      b. Identify rtPA candidates beyond the normal time window
      c. Assess cerebral tissue viability, which can aid in determining the time of infarction
         i. DWI detects cytotoxic edema within the brain by observing reduced permeability of extracellular water within minutes of an ischemic event
         ii. FLAIR detects vasogenic edema in the brain which begins to develop in the hours following an ischemic event

III. Stroke severity score28
    a. National Institutes of Health Stroke Severity (NIHSS) scale (Appendix B)
       i. Widely used scale both in medical facilities and clinical trials
       ii. Initial stroke presentation is graded for a baseline score
          1. Baseline score strongly predicts overall outcome
             a. Lower the score=better the outcome
             b. Scores range from 0 to 42 points
          2. Addition of one point decreases the likelihood of an excellent post-stroke outcome
             a. At seven days → 24% decrease
b. At three months $\rightarrow$ 17% decrease

3. Outcome predictions
   a. NIHSS < 14 $\rightarrow$ 80% of patients expected to have good outcomes
   b. NIHSS > 20 $\rightarrow$ 20% of patients expected to have good outcomes

4. Post-hospital placement
   a. Severe (NIHSS $\geq$ 14) $\rightarrow$ long term care facility
   b. Moderate (NIHSS 6-13) $\rightarrow$ acute inpatient rehabilitation
   c. Mild (NIHSS $\leq$ 5) $\rightarrow$ discharged directly home (~80%) with or without home health

   iii. Periodic reassessment determines stroke symptom improvement
   iv. Improvement defined as an NIHSS score decreases by $\geq$ 4 points

Table 2. NIHSS Score Interpretation

<table>
<thead>
<tr>
<th>Stroke severity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of stroke</td>
<td>0</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>1 to 4</td>
</tr>
<tr>
<td>Moderate stroke</td>
<td>5 to 15</td>
</tr>
<tr>
<td>Moderate to severe stroke</td>
<td>16 to 20</td>
</tr>
<tr>
<td>Severe stroke</td>
<td>21 to 42</td>
</tr>
</tbody>
</table>

Ischemic Stroke Treatment Recommendations $^{1,5,29-39}$

I. 2013 guidelines for the early management of acute ischemic stroke treatment indications $^{1,2,29}$
   a. Treatment options for acute ischemic strokes are based upon inclusion/exclusion identified via radiographic studies

   Figure 5. Intracranial Findings on NECT Exam

   Early ischemic changes $\checkmark$ thrombolysis candidate
   - Hypodensity (darkened area) on NECT
   - Less dense brain tissue on scan due to decreased blood flow

   Hemorrhage $\times$ thrombolysis candidate
   - Hyperintensity (white area) on NECT
   - Bright white appearance due to the presence of blood

   Old infarct $\times$ thrombolysis candidate
   - Frank hypodensity (dark area) on NECT
   - Unlikely to benefit from IV thrombolysis

   $>$1/3 middle cerebral artery (MCA) territory $\times$ thrombolysis candidate
   - Hypodensity (dark area) on NECT
   - Large infarct associated with higher risks

II. Treatment $^{3-5}$
   a. Overview $^{10-32}$
      i. Evaluation for recombinant tissue plasminogen activator (rtPA) eligibility
         1. NECT scan to identify patients with early ischemic changes and rule out hemorrhage
         2. Stroke mimics
            a. Glucose measurement
               i. Rule out hypoglycemia as a cause of stroke-like symptoms
               ii. Poorer outcomes in hyperglycemic patients
         3. History to establish timeline of stroke and identify factors that would preclude the use of rtPA
         4. Inclusion/exclusion criteria
         5. Blood pressure measurement
b. Acute management

<table>
<thead>
<tr>
<th>Emergency department-based care goals</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to physician</td>
<td>≤ 10 minutes</td>
</tr>
<tr>
<td>Door to stroke team</td>
<td>≤ 15 minutes</td>
</tr>
<tr>
<td>Door to CT initiation</td>
<td>≤ 25 minutes</td>
</tr>
<tr>
<td>Door to CT interpretation</td>
<td>≤ 45 minutes</td>
</tr>
<tr>
<td>Door to rtPA</td>
<td>≤ 60 minutes</td>
</tr>
<tr>
<td>Door to stroke unit admission</td>
<td>≤ 180 minutes</td>
</tr>
</tbody>
</table>

c. Intravenous (IV) thrombolytic therapy with rtPA

i. Mechanism of thrombolysis

1. Converts plasminogen to plasmin and ultimately helps dissolve blood clot, allowing the re-establishment of blood flow through the cerebral vasculature

Figure 6. Mechanism of rtPA

<table>
<thead>
<tr>
<th>Mechanism of rtPA (alteplase) binds to fibrin in thrombus</th>
<th>Converts entrapped plasminogen to plasmin that initiates local fibrinolysis.</th>
</tr>
</thead>
</table>

i. Dosing

1. 0.9 mg/kg IV (max 90 mg) dosed on actual body weight
   a. 10% is administered via IV push over one minute
   b. 90% is infused over the remaining hour

ii. Inclusion and exclusion criteria (full criteria can be found in Appendix C)

1. Age >18 years old
2. Ischemic stroke seen on NECT
3. No hemorrhage identified

iv. Time to needle

1. Early treatment with rtPA is associated with better outcomes
2. Benefit from IV rtPA depends on timing of administration post-stroke
   a. 90-minutes post-stroke → greatest benefit
   b. 91 minutes to 180-minutes post-stroke → benefit
   c. 181 minutes to 270-minutes post-stroke → modest benefit

v. Adverse effects

1. Angioedema
   a. Definition
      i. Bilateral or unilateral tongue and face swelling and edema
      ii. Unilateral edema most likely on the opposite side of affected hemisphere
   b. Occurrence
      i. Reported rates 1.3-5.1%
      ii. Risk of occurrence increases with concomitant angiotensin converting enzyme inhibitor use, frontal, and insular strokes

2. Hemorrhagic transformation
   a. Definition
      i. National Institute of Neurological Disorders and Stroke (NINDS) defined it as sICH as a CT-documented hemorrhage within 36 hours of treatment and was temporally related to decline in the patient’s clinical condition; decline in clinical condition was based on the judgement of the clinical investigator
      ii. European Cooperative Acute Stroke Study (ECASS III) defined it as sICH as CT or MRI-documented hemorrhage associated with an increase of at least 4 points on NIHSS score
b. Classifications of hemorrhage

Table 4. Classification of Symptomatic Intracerebral Hemorrhage (sICH)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Radiographic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic infarction</td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>Small; hyperdense petechiae</td>
</tr>
<tr>
<td>Type 2</td>
<td>Confluent hyperdensity within infarct zone; no mass effect</td>
</tr>
<tr>
<td>Parenchymal infarction</td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>Hyperdensity &lt;30% of infarct zone; some mass effect</td>
</tr>
<tr>
<td>Type 2</td>
<td>Hyperdensity &gt;30% of infarct zone; significant mass effect</td>
</tr>
</tbody>
</table>

Mass effect = hematoma causing significant swelling/increased intracranial pressure that can result in herniation on midline shift.

c. Hemorrhage occurrence

i. Within 3 hours of symptom onset
1. 6.4% rtPA versus 0.6% placebo treated patients (NINDS definition)

ii. Within 4.5 hours of symptom onset
1. 2.4% rtPA versus 0.2% placebo treated patients (ECASS III definition)
2. 7.9% rtPA versus 3.5% placebo treated patients (NINDS definition)

iii. Other literature
1. 5-6% of sICH after rtPA administration

d. More commonly occurs in patients with

i. Evidence of mass effect or early clear hypodensity

ii. Hypoattenuation >1/3 MCA territory on baseline NECT

iii. Larger strokes

iv. Older age

v. Cardioembolic-induced stroke

e. Steps to minimize risk and sequelae of transformation

i. Tight blood pressure control

ii. Immediate head CT with any mental status deterioration

iii. Neurological status checks regularly

Wake Up Ischemic Stroke (WUS)\texttrademark,\textsuperscript{1,6,22,40-45}

I. Introduction to WUS
   a. Definition\textsuperscript{1}
      i. An ischemic (or hemorrhagic) stroke that presents upon awakening from sleep
      ii. Unknown time of symptom onset
   b. Epidemiology\textsuperscript{6,22,40}
      i. Annually, approximately 25% of strokes are realized upon awakening from sleep
      ii. Numerous clinical trials have shown the predominance of strokes occurring in the morning hours
      iii. Clinical characteristics of WUS and non-WUS are indistinguishable

II. Pathophysiology\textsuperscript{22,42,43}
   a. Presentation is indistinguishable from strokes with known-onset times
   b. Predisposing factors for ischemic stroke during sleep
      i. Cerebral blood flow alterations due to circadian rhythm \(\rightarrow\) hemodynamic variations + vascular stenosis
      ii. Hemodynamic variations during sleep may lead to cerebral ischemia \(\rightarrow\) reduced heart rate, blood pressure, metabolic drive, and sympathetic drive
      iii. Obstructive sleep apnea \(\rightarrow\) hypoxic episodes

III. WUS hypothesis
   a. Patients may be awakening due to the onset of stroke, as opposed to waking up several hours after stroke occurrence

IV. Imaging\textsuperscript{44,45}
   a. CT and MRI evidence in WUS patients who arrive within 4 hours of waking are indistinguishable from that of patients with known onset time imaging within 4 hours
      i. Similar findings on NECT using ASPECTS grading suggests the possibility of rtPA intervention in these clinically indistinguishable patients
      ii. CTP is currently being used in clinical trials to better determine the time of stroke onset and extend the off-label use of thrombolysis for WUS patients
      iii. DWI-FLAIR mismatch has also been used to extend the time window for patients to receive thrombolytic therapy
         1. Ischemic lesions evolve and become clearly evident beyond 3 hours from symptom onset
WUS Treatment Recommendations

I. Treatment
   a. Currently there are no treatments specifically indicated to treat WUS
   b. WUS patients are excluded from potentially life-saving or quality-of-life-saving rtPA thrombolytic therapy

II. Lack of high-level literature exists to support any therapeutic intervention
   a. Proposed treatments are based upon retrospective reviews and observational studies
   b. Conflicting results
      i. Similar rates of sICH in WUS compared to known-onset stroke patients treated with rtPA
      ii. ABESTT-II found increased hemorrhagic transformation in WUS patients compared to known-onset stroke patients
         1. This randomized controlled trial investigated the use of abciximab in WUS patients
         2. Many clinicians have extrapolated these findings to exclude the use of IV rtPA in this subset of patients

III. Lack of standardized evaluation and treatment has led to a boom in wake up stroke clinical trials

Literature for Intravenous tPA in Wake Up Strokes


Objective
   • Demonstrate safety of IV rtPA in patients with WUS

Design
   • Prospective, single-arm, multicenter, open-label safety study with a pragmatic design requiring only NECT
   • Independent DSMB and a pre-specified safety monitoring plan defined as sICH <10% (if sICH >10% then trial must stop)

Patient Population

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age 18-80 years with NIHSS ≤25 with signed consent form</td>
<td>• FDA approved exclusion criteria (Appendix C)</td>
</tr>
<tr>
<td>• Ischemic stroke during sleep</td>
<td>• Planned endovascular intervention</td>
</tr>
</tbody>
</table>

Intervention

<table>
<thead>
<tr>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>• IV rtPA 0.9 mg/kg (maximum 90 mg): 10% bolus over 1 minute and 90% infused over 60 minutes</td>
</tr>
<tr>
<td>• rtPA bolus within 3 hours of waking with symptoms</td>
</tr>
</tbody>
</table>

Outcomes

• Primary safety endpoint → frequency of sICH within 24 hours after treatment
  o sICH = ICH present on CT temporally related to decline in NIHSS of ≥4 points within 24 hours of rtPA
• Secondary endpoints
  o Asymptomatic ICH and rates of type-2 parenchymal hematoma
  o Clinical improvements in NIHSS
  o Clinical improvements in 90-day mRS score

Methods
   • Prospective analysis taking place between October 2010 and October 2013 from 5 stroke centers

Baseline Characteristics | Results
--- | ---
Age, mean (±SD) | 60.8 (±13.2)
Male, n (%) | 20 (50%)
Race/ethnicity, n (%) | 
Caucasian | 17 (42.5%)
Hispanic | 6 (15%)
African American | 16 (40%)
Asian | 1 (2.5%)
Medical history, n (%) | 
Past stroke or transient ischemic attack | 10 (25%)
Hypertension | 30 (75%)
Diabetes mellitus | 18 (45%)
Atrial fibrillation | 7 (18%)
Coronary artery disease | 5 (13%)
Hyperlipidemia | 15 (38%)

Prestroke mRS, n (%) | 
0 or 1 | 36 (90%)
2 | 3 (7.5%)
3 | 1 (2.5%)
NIHSS, median (IQR) | 6.5 (4, 10.5)
Glucose, median (range) | 125.5 (104, 169)
INR, median (IQR) | 0.99 (0.94, 1.04)

ASPECTS score
Mean (±SD) | 9 (±1.7)
Median (range) | 10 (4-10)
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
</tr>
<tr>
<td>sICH frequency within 24 hours, n (%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Secondary endpoint, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Total asymptomatic ICH</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Type 1 hemorrhagic transformation</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Type 2 hemorrhagic transformation</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Type 1 or 2 parenchymal hematoma</td>
<td>0</td>
</tr>
<tr>
<td><strong>Adverse events (reported in 30 of the total 40 patients)</strong></td>
<td></td>
</tr>
<tr>
<td>Total adverse events documented, n</td>
<td>113</td>
</tr>
<tr>
<td>Serious adverse events, n</td>
<td>8</td>
</tr>
<tr>
<td>DSMB adjudicated events and relatedness to rtPA, n</td>
<td>12</td>
</tr>
<tr>
<td>Possibly</td>
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</tr>
<tr>
<td>Asymptomatic ICH, n</td>
<td>6</td>
</tr>
<tr>
<td>Persistently elevated prothrombin time, n</td>
<td>3</td>
</tr>
<tr>
<td>Probably</td>
<td></td>
</tr>
<tr>
<td>External ear hemorrhage, n</td>
<td>1</td>
</tr>
<tr>
<td>Definitely</td>
<td></td>
</tr>
<tr>
<td>Orolingual angioedema, n</td>
<td>2</td>
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<tr>
<td><strong>Deaths</strong></td>
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</tr>
<tr>
<td>Septic shock</td>
<td>1</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>1</td>
</tr>
<tr>
<td><strong>Discharge diagnosis of stroke mimic</strong></td>
<td></td>
</tr>
<tr>
<td>Hemiplegic migraine</td>
<td>2</td>
</tr>
<tr>
<td>Conversion disorder</td>
<td>1</td>
</tr>
<tr>
<td>Brain neoplasm</td>
<td>1</td>
</tr>
</tbody>
</table>

**Conclusions**
- IV thrombolysis with rtPA appears to be safe in WUS patients selected by NECT

**Strengths**
- Pilot study for safety analysis
- Independent DSMB
- Mimic rates <10% and consistent rates with other studies
- Investigated outcomes widely reported in the literature
- Utilized standard inclusion/exclusion criteria
- Pragmatic design utilizing only NECT for thrombolysis

**Limitations**
- Small sample size that took 3 years to recruit 40 patients—may underestimate predominance of WUS
- Selection bias of patients included in the study
- Prespecified statistical power not established to evaluate whether treatment was safe or not
- Low stroke severity scores
- Lack of efficacy assessment and outcomes

**Funding**
- Partially supported by Genentech Inc.

**Take Home Points**
- Specific WUS patients may be able to be treated safely with rtPA when utilizing strict imaging, inclusion, and exclusion criteria
- Raw numbers of the safety data appear comparable to other similar studies but caution with generalization to all WUS patients because this study was not powered to detect whether or not treatment was safe

ASAPECTS=Alberta Stroke Program Early Computed Tomography; CT=computed tomography; DSMB=data safety monitoring board; ED=emergency department; FDA=Food and Drug Administration; ICH=intracerebral hemorrhage; IQR=interquartile range; IV=intravenous; mRS=modified Rankin Scale score; NECT=noncontrast-enhanced computed tomography; NIHSS=National Institutes of Health Stroke Scale; rtPA=recombinant tissue plasminogen activator; SD=standard deviation; sICH=symptomatic intracerebral hemorrhage; WUS=wake up stroke


#### Objective
- Determine the clinical significance of rtPA in WUS patients

#### Study Design
- Propensity-matched analysis of WUS patients treated with IV rtPA versus no treatment

#### Patient Population
- Last seen normal before going to sleep
- Either witnessed with stroke symptoms upon waking or waking with symptoms after sleeping ≥ 3 hours
- Inclusion criteria for rtPA within 4.5 hours (Appendix C)

#### Intervention
- Non-WUS given rtPA within 4.5h
- IV rtPA 0.9 mg/kg with 10% bolus over 1 minute and 90% infusion over 60 minutes

#### Controls
- WUS with off-label rtPA treatment
- IV rtPA 0.9 mg/kg with 10% bolus over 1 minute and 90% infusion over 60 minutes
- Signed informed consent

#### Treated WUS
- IV rtPA 0.9 mg/kg with 10% bolus over 1 minute and 90% infusion over 60 minutes

#### Non-treated WUS
- Non-treated WUS

#### Outcomes
- Primary safety endpoint
  - Development of sICH present on NECT 24-hours post rtPA infusion
  - sICH defined as ICH on CT + temporally related to decline in NIHSS of ≥ 4 points within 24-hours post-hospitalization

#### Missing/unknown baseline demographics or OSH transfer
- Off-label rtPA (>4.5 hours and not WUS)
- Endovascular intervention
- FDA approved exclusion criteria (Appendix C)
## Methods

- Stroke registry between July 2008 and May 2014 with retrospective identification of consecutive patients meeting inclusion criteria
- Classified into three different groups
  - (I) Stroke onset <4.5 hours + rtPA (control group; n=369)
  - (II) WUS + rtPA (n=46)
  - (III) WUS – rtPA (n=154)

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control (I) (n=369)</th>
<th>WUS+rtPA (II) (n=46)</th>
<th>P-value (I vs II)</th>
<th>WUS–rtPA (III) (n=154)</th>
<th>P-value (II vs III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>64 (22-102)</td>
<td>69 (42-98)</td>
<td>0.107</td>
<td>63 (22-93)</td>
<td>0.146</td>
</tr>
<tr>
<td>Female</td>
<td>49.3%</td>
<td>52.2%</td>
<td>0.715</td>
<td>48.8%</td>
<td>0.379</td>
</tr>
<tr>
<td>African American</td>
<td>62.9%</td>
<td>73.3%</td>
<td>0.168</td>
<td>70.8%</td>
<td>0.739</td>
</tr>
<tr>
<td><strong>Past medical history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12%</td>
<td>13%</td>
<td>0.841</td>
<td>13.6%</td>
<td>0.918</td>
</tr>
<tr>
<td>Diabetes</td>
<td>29%</td>
<td>43.5%</td>
<td>0.044</td>
<td>29.2%</td>
<td>0.070</td>
</tr>
<tr>
<td>Hypertension</td>
<td>76.6%</td>
<td>78.3%</td>
<td>0.805</td>
<td>77.3%</td>
<td>0.889</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>39%</td>
<td>41.3%</td>
<td>0.765</td>
<td>39%</td>
<td>0.833</td>
</tr>
<tr>
<td>CHF</td>
<td>18.6%</td>
<td>15.6%</td>
<td>0.679</td>
<td>11.4%</td>
<td>0.514</td>
</tr>
<tr>
<td>Admission NIHSS, median (range)</td>
<td>8 (0-39)</td>
<td>9.5 (1-27)</td>
<td>0.528</td>
<td>5 (0-33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Stroke etiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>27.6%</td>
<td>23.9%</td>
<td></td>
<td>22.2%</td>
<td>0.855</td>
</tr>
<tr>
<td>Large vessel</td>
<td>17.9%</td>
<td>17.4%</td>
<td></td>
<td>17.7%</td>
<td></td>
</tr>
<tr>
<td>Small vessel</td>
<td>8.9%</td>
<td>6.5%</td>
<td></td>
<td>34.6%</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>35%</td>
<td>37%</td>
<td></td>
<td>16.3%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10.6%</td>
<td>15.2%</td>
<td></td>
<td>9.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Coagulation, median (range)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>1(0.7-3.1)</td>
<td>1 (0.9-1.4)</td>
<td>0.761</td>
<td>1 (0.9-3.1)</td>
<td>0.597</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>40.1(15.1-52.8)</td>
<td>38.6 (23.3-51.4)</td>
<td>0.074</td>
<td>39.25 (21.5-54.6)</td>
<td>0.599</td>
</tr>
<tr>
<td>Platelets</td>
<td>217 (71-751)</td>
<td>216 (131-515)</td>
<td>0.981</td>
<td>231.5 (119-531)</td>
<td>0.205</td>
</tr>
<tr>
<td>Glucose</td>
<td>119 (78-569)</td>
<td>118 (64-345)</td>
<td>0.777</td>
<td>117 (74-574)</td>
<td>0.730</td>
</tr>
</tbody>
</table>

### Results

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Control (I) (n=369)</th>
<th>WUS+rtPA (II) (n=46)</th>
<th>P-value (I vs II)</th>
<th>WUS–rtPA (III) (n=154)</th>
<th>P-value (II vs III)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sICH at 24 hours</td>
<td>3%</td>
<td>2.2%</td>
<td>0.758</td>
<td>0.7%</td>
<td>0.362</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS after 24h, median (range)</td>
<td>4 (0-42)</td>
<td>4 (0-26)</td>
<td>0.173</td>
<td>3 (0-29)</td>
<td>0.225</td>
</tr>
<tr>
<td>Δ neuro ≥2 NIHSS</td>
<td>27.7%</td>
<td>30.4%</td>
<td>0.6999</td>
<td>29.2%</td>
<td>0.874</td>
</tr>
<tr>
<td>Δ NIHSS from 0-24h, median (range)</td>
<td>-3 (-39 to 36)</td>
<td>-2 (-16 to 19)</td>
<td>0.621</td>
<td>-1 (-13 to 17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mRS at discharge, median (range)</td>
<td>3 (0-6)</td>
<td>3 (0-6)</td>
<td>0.771</td>
<td>3 (0-6)</td>
<td>0.322</td>
</tr>
<tr>
<td>Good outcome (mRS 0-2)</td>
<td>49.9%</td>
<td>47.8%</td>
<td>0.794</td>
<td>42.9%</td>
<td>0.551</td>
</tr>
<tr>
<td>Favorable d/c disposition</td>
<td>67.5%</td>
<td>69.6%</td>
<td>0.775</td>
<td>71.4%</td>
<td>0.471</td>
</tr>
<tr>
<td>Discharge NIHSS, median (range)</td>
<td>2 (0-42)</td>
<td>3 (2-42)</td>
<td>0.532</td>
<td>3 (0-42)</td>
<td>0.395</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>6.8%</td>
<td>4.4%</td>
<td>0.529</td>
<td>3.9%</td>
<td>0.891</td>
</tr>
</tbody>
</table>

### Conclusions

- Higher evidence of favorable outcomes in rtPA treated WUS patients compared to those left untreated
- Failed to show a statistically significant difference in mortality between the two groups

### Critique

- Compared WUS+rtPA treatment against controls receiving rtPA and also against WUS patients without rtPA treatment
- Propensity score matching: based on likelihood of WUS patients receiving rtPA

### Limitations

- Power calculation for sample size was not initially performed
- Retrospective power calculation determined that sample size for both groups would be 6002 patients to reach 80% power

### Funding

- One author is compensated by Genentech Inc. through participation in the speaker's bureau

### Take Home Points

- Caution with generalizability due to being a retrospective, single-center, nonrandomized design
- rtPA may be an option to offer when clinically appropriate
- Comparable rates of sICH between WUS and known-onset stroke patients treated with rtPA
- Superior outcomes in WUS treated patients versus those who received no treatment

\( \Delta \) change; CHF=congestive heart failure; CT=computed tomography; d/c=discharge; FDA=Food and Drug Administration; 24h=twenty-four hours; ICH=intracerebral hemorrhage; INR=international normalized ratio; IV=intravenous; MCA=middle cerebral artery; mRS=modified Rankin Scale score; NECT=noncontrast enhanced computed tomography; NIHSS=National Institutes of Health stroke scale; OSH=outside hospital; rtPA=recombinant tissue plasminogen activator; sICH=symptomatic intracerebral hemorrhage; WUS=wake up stroke

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Purpose

- A priori hypothesis that WUS patients meeting all other criteria will have better outcomes after rtPA treatment compared to those who did not receive treatment for WUS any treatment for their ischemic stroke

Study Design

- Observational study, consecutive sampling of prospective registry at tertiary stroke center

Patient Population

- Last seen normal in <12 hours or >4.5 hours
- No deficits when last awake but witnessed deficits upon waking
- Inclusion criteria for rtPA within 4.5 hours (Appendix C)

Exclusion

- NECT scan with
  - >1/3 MCA territory involvement
  - Multiple territory involvement
  - Established infarction (defined lesion markers)

Intervention

- WUS patients treated with IV rtPA after signing informed consent presents in <4.5 hours and otherwise a rtPA candidate
- Assessed at arrival for baseline NIHSS and NECT scans assessed using ASPECTS to assess for early ischemic changes
- CTP not required in 64 of 122 (52%) patients immediately after NECT no pre-specified mismatch-based criteria existed
- Standard rtPA dosing utilized and patients monitored
- Off-Label use of rtPA (with consent) approved by Novel Procedures and Therapeutics Committee of the Institution

Outcomes

- Primary endpoint
  - mRS score (0-2) assessed at 90 days
- Secondary endpoints
  - Mortality
  - sICH on follow-up CT classified by ECASS II classifications

Methods

- Patients enrolled between January 2009 and December 2010
- All patient data is prospectively gathered
- Data was verified against CT images and medical records to ensure accuracy and completeness
- Stroke pathogenesis determined and categorized after medical record review and record investigation completed by two independent investigators

Baseline Characteristics (n=122)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>WUS treated (n=68)</th>
<th>WUS non-treated (n=54)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>73.9 (15.6)</td>
<td>70.6 (16.7)</td>
<td>0.152</td>
</tr>
<tr>
<td>Men, n</td>
<td>23 (34%)</td>
<td>28 (52%)</td>
<td>0.064</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>45 (66%)</td>
<td>32 (59%)</td>
<td>0.432</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>14 (21%)</td>
<td>13 (24%)</td>
<td>0.645</td>
</tr>
<tr>
<td>Dyslipidemia, n</td>
<td>22 (32%)</td>
<td>25 (46%)</td>
<td>0.214</td>
</tr>
<tr>
<td>Atrial fibrillation, n</td>
<td>21 (31%)</td>
<td>9 (17%)</td>
<td>0.070</td>
</tr>
<tr>
<td>Current smoker, n</td>
<td>8 (12%)</td>
<td>7 (13%)</td>
<td>0.686</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD)</td>
<td>152 (26)</td>
<td>153 (28)</td>
<td>0.951</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD)</td>
<td>84 (20)</td>
<td>85 (18)</td>
<td>0.669</td>
</tr>
<tr>
<td>Glucose, mean (SD)</td>
<td>6.5 (2.4)</td>
<td>7.1 (3.3)</td>
<td>0.344</td>
</tr>
<tr>
<td>NIHSS, median (IQR)</td>
<td>11.5 (8-17)</td>
<td>9 (5-15)</td>
<td>0.034</td>
</tr>
<tr>
<td>Posterior circulation stroke, n</td>
<td>9 (13%)</td>
<td>8 (15%)</td>
<td>0.802</td>
</tr>
<tr>
<td>ASPECTS 8-10, n</td>
<td>57 (84%)</td>
<td>38 (70%)</td>
<td>0.075</td>
</tr>
<tr>
<td>Hyperdense artery sign, n</td>
<td>28 (41%)</td>
<td>17 (32%)</td>
<td>0.270</td>
</tr>
<tr>
<td>CTP, n</td>
<td>45 (66%)</td>
<td>19 (35%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mismatch on CTP, n</td>
<td>18/45 (40%)</td>
<td>0</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Pathogenicity, n

<table>
<thead>
<tr>
<th>Pathogenicity</th>
<th>WUS treated (n=68)</th>
<th>WUS non-treated (n=54)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic</td>
<td>14 (21%)</td>
<td>6 (11%)</td>
<td>0.060</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>33 (48%)</td>
<td>21 (39%)</td>
<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>4 (6%)</td>
<td>12 (22%)</td>
<td></td>
</tr>
<tr>
<td>Other determined</td>
<td>4 (6%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Undetermined/mixed pathogenicity</td>
<td>13 (19%)</td>
<td>13 (24%)</td>
<td></td>
</tr>
</tbody>
</table>

Outcomes

<table>
<thead>
<tr>
<th>Results (n=122)</th>
<th>WUS treated (n=68)</th>
<th>WUS non-treated (n=54)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoints, n</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent (mRS 0 to 1 at 90 days)</td>
<td>11 (16.2%)</td>
<td>5 (9.3%)</td>
<td>0.494</td>
</tr>
<tr>
<td>Good (mRS 0 to 2 at 90 days)</td>
<td>25 (36.8%)</td>
<td>14 (25.9%)</td>
<td>0.346</td>
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<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality at 90 days, n</td>
<td>10 (14.7%)</td>
<td>14 (25.9%)</td>
<td>0.122</td>
</tr>
<tr>
<td>NIHSS at 24 hours, median (IQR)</td>
<td>6 (2, 13.5)</td>
<td>5 (3, 10)</td>
<td>0.82</td>
</tr>
<tr>
<td>NIHSS change in 24 hours, median (IQR)</td>
<td>-4 (-8, 0)</td>
<td>-3 (-4, 0)</td>
<td>0.14</td>
</tr>
<tr>
<td>sICH by ECASS II criteria, n</td>
<td>2 (2.9%)</td>
<td>0</td>
<td>0.204</td>
</tr>
<tr>
<td>Any ICH, n</td>
<td>15 (22.1%)</td>
<td>2 (3.7%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Conclusions

- Preliminary study suggesting rtPA in specific WUS patients based on clinical/imaging criteria is feasible and may have better outcomes
Critique

Strengths

• Differences in outcomes were all consistently favoring thrombolysis and were confirmed in analysis when adjusted for NIHSS scores
• Potential sampling bias minimized through the use of specific inclusion criteria and consecutive sampling of an ongoing registry
• Bias caused by incomplete/incorrect data was minimized by using standardized definitions, validated scales, and source data verification
• Assessments of outcomes were performed by certified and trained observers that had no involvement in patient care
• Various analyses were pre-specified and regression models were used to adjust for potential differences in baseline covariates when assessing outcomes

Limitations

• Small sample size
• Milder stroke score in non-treated WUS patients may have limited ability to achieve significance
• Inadvertent bias favoring IV rtPA treatment may have occurred in patients with lower recovery potential not consenting for high-risk unproven treatment; only 9 patients refused to consent to treatment
• CTP imaging is a potential source of bias because WUS patients may be more likely to get a CTP to ensure they are the most appropriate candidate to get therapy
• Unmeasured bedside bias secondary to clinical judgment in case selection for thrombolysis

Funding

• Institutional grant from King’s College Hospital Foundation Trust Research and Development Program

Take Home Points

• Single-center observational study showing clinically significant benefits in appropriate WUS patients treated with rtPA
• Offering rtPA to select patients may be warranted based on clinical picture and imaging

ASPECTS= Alberta Stroke Program Early Computed Tomography Score; CT=computed tomography; CTP=computed tomography perfusion; ECASS= European Cooperative Acute Stroke Study; ICH= intracerebral hemorrhage; ICU= intensive care unit; IQR= interquartile range; IV= intravenous; MCA= middle cerebral artery; mRS= modified Rankin Scale score; NECT= noncontrast-enhanced computed tomography; NIHSS= National Institutes of Health Stroke Scale; rtPA= recombinant tissue plasminogen activator; SD= standard deviation; sICH= symptomatic intracerebral hemorrhage; WUS= wake-up stroke


Hypothesis

• WUS patients with no or early ischemic changes on neuroimaging will have comparable outcomes to patients getting IV rtPA with known onset of stroke

Study Design

• Observational study, consecutive sampling of prospective registry at tertiary stroke center

Inclusion

• LSN <12 hours or >4.5 hours after onset of symptoms
• No neurological deficits when last awake
• Witnessed deficits upon wakening
• Presented to hospital emergently
• Inclusion criteria for rtPA within 4.5 hours (Appendix C)

Exclusion

• CT with >1/3 MCA territory involvement
• CT showing multiple territory involvement
• CT showing established infarction
• NIHSS <5

Intervention

• IV rtPA 0.9 mg/kg with 10% bolus over 1 minute and 90% infusion over 60 minutes (maximum 90 mg total)

Outcomes

• Primary endpoint → mRS score (0-2) assessed at 90 days
• Secondary endpoints → mortality and sICH on follow-up CT classified by ECASS classifications

Methods

• Patients enrolled between January 2009 and December 2010
• All patient data is prospectively gathered
• Data was verified against CT images and medical records to ensure accuracy and completeness
• Stroke pathogenesis determined and categorized after medical record review and record investigation completed by two independent investigators

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>WUS treated (n=68)</th>
<th>Reference group (n=326)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>73.9 (15.6)</td>
<td>72.8 (14.7)</td>
<td>0.58</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>23 (34%)</td>
<td>155 (48%)</td>
<td>0.045</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>45 (66%)</td>
<td>185 (57%)</td>
<td>0.38</td>
</tr>
</tbody>
</table>
Diabetes mellitus, n (%) | 14 (21%) | 54 (17%) | 0.48
Dyslipidemia, n (%) | 22 (32%) | 95 (29%) | 0.14
Atrial fibrillation, n (%) | 21 (31%) | 79 (24%) | 0.28
Cardiac comorbidity, n (%) | 23 (34%) | 90 (28%) | 0.38
Current smoker, n (%) | 8 (12%) | 43 (13%) | 0.85
Systolic blood pressure, mean (SD) | 152 (26) | 150 (26) | 0.58
Diatolic blood pressure, mean (SD) | 84 (20) | 85 (17) | 0.51
Glucose, mean (SD) | 6.5 (2.4) | 6.5 (2.7) | 0.79
NIHSS, median (IQR) | 12 (8-17) | 13 (7-15) | 0.34
Posterior circulation stroke, n (%) | 9 (13%) | 27 (8%) | 0.24
ASPECTS 8-10, n (%) | 57 (84%) | 262 (80%) | 0.33
Hyperdense artery sign, n (%) | 28 (41%) | 148 (45%) | 0.69
CTP, n (%) | 45 (66%) | 84 (26%) | <0.0001
Door to CT, median | 41 min | 42 min | 0.93
Door to needle, median | 73 min | 60 min | 0.14

Pathogenesis
Atherosclerotic, n (%) | 14 (21%) | 34 (10%) | 0.023
Cardioembolic, n (%) | 33 (48%) | 148 (45%)
Lacunar, n (%) | 4 (6%) | 52 (16%)
Other determined, n (%) | 4 (6%) | 16 (5%)
Undetermined/mixed, n (%) | 13 (19%) | 76 (23%)

Results

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>WUS treated (n=68)</th>
<th>Reference group (n=326)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoints, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent (mRS 0-1 at 90 days)</td>
<td>11 (16%)</td>
<td>77 (24%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Good (mRS 0-2 at 90 days)</td>
<td>25 (37%)</td>
<td>124 (38%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality at 90 days, n (%)</td>
<td>10 (15%)</td>
<td>82 (26%)</td>
<td>0.06</td>
</tr>
<tr>
<td>NIHSS at 24 hours, median (IQR)</td>
<td>6 (2-14)</td>
<td>9 (3-13)</td>
<td>0.26</td>
</tr>
<tr>
<td>NIHSS change in 24 hours, median</td>
<td>-4</td>
<td>-4</td>
<td>0.53</td>
</tr>
<tr>
<td>sICH by ECASS II criteria, n (%)</td>
<td>2 (2.9%)</td>
<td>11 (3.4%)</td>
<td>1</td>
</tr>
<tr>
<td>Any ICH, n (%)</td>
<td>15 (22%)</td>
<td>66 (20%)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Conclusions
- No significant differences exist between WUS patients receiving rtPA versus those left untreated; thrombolysis in selected WUS patients has comparable outcomes to those of known-onset stroke times treated with rtPA
- Findings remained despite adjusting for sex, age, diabetes, atrial fibrillation, blood pressure, blood glucose, stroke pathogenesis, CTP use or mismatch analysis, NIHSS score

Critique
- Strengths:
  - Selection bias minimized by
    - Predefined selection criteria
    - Consecutive patients meeting criteria included
  - Registry data were collected prospectively
  - Standardized definitions/scales used to assess baseline characteristics, stroke severity, and outcomes
  - Images reviewed by trained physicians unaware of patient group being analyzed
  - Outcomes assessed by outside observers
  - Data analyses were prespecified
  - 2% (9/394) patients lost to follow-up at 90 days
- Limitations:
  - Bias in
    - Patient selection
    - Recording
    - Completeness of data
    - Assessments of outcomes
  - CTP use in WUS patients → favoring good outcomes
  - CTP in small number of patients
  - Limitations in techniques used to assess perfusion mismatch on CTP
  - Bedside bias because of clinical judgment

Funding
- Institutional grant from King’s College Hospital Foundation Trust Research and Development Program
Take Home Points
- No statistically significant differences between WUS treatment group and reference group
- Possibility of safely treating WUS patients with IV rtPA when identified and selected based on specific/strict criteria

ASPECTS=Alberta Stroke Program Early Computed Tomography Score; CT=computed tomography; CTP=computed tomography perfusion; ECASS=European Cooperative Acute Stroke Study; h=hours; ICH=intracerebral hemorrhage; IQR=interquartile range; IV=intravenous; LSN=last seen normal; MCA=middle cerebral artery; mRS=modified Rankin Scale score; NECT=noncontrast-enhanced computed tomography; NIHSS=National Institutes of Health stroke scale; rtPA=recombinant tissue plasminogen activator; SD=standard deviation; sICH=symptomatic intracerebral hemorrhage; WUS=wake up stroke

Summary of Evidence

Table 5. Summary of Literature

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>rtPA 0.9 mg/kg (max 90 mg)</td>
<td>rtPA 0.9 mg/kg (max 90 mg)</td>
<td>rtPA 0.9 mg/kg (max 90 mg)</td>
<td>rtPA 0.9 mg/kg (max 90 mg)</td>
</tr>
<tr>
<td>Subjects</td>
<td>Within 3 hours of waking</td>
<td>Within 4.5 hours of waking</td>
<td>Within 4.5 hours of waking</td>
<td>Within 4.5 hours of waking</td>
</tr>
<tr>
<td>Enrollment</td>
<td>WUS n=40</td>
<td>Control n=369</td>
<td>WUS treated n=68</td>
<td>WUS treated n=68</td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td>sICH within 24 hours</td>
<td>WUS+rtPA n=46</td>
<td>WUS normal n=54</td>
<td>Reference group n=326</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td>aICH, major bleeding, NIHSS improvements, mRS at 90d</td>
<td>NIHSS at 24h, neurological deterioration, NIHSS change 0-24h, mRS at discharge, good functional outcome, discharge NIHSS, mortality</td>
<td>Mortality, sICH score</td>
<td>Mortality, sICH score</td>
</tr>
<tr>
<td>Imaging Utilized</td>
<td>NECT</td>
<td>NECT</td>
<td>NECT</td>
<td>NECT</td>
</tr>
<tr>
<td>Conclusions</td>
<td>IV rtPA appears safe in WUS patients selected by NECT</td>
<td>Higher evidence of favorable outcomes in WUS treated with rtPA versus untreated</td>
<td>Thrombolysis in WUS patients is feasible and associated with better outcomes</td>
<td>Thrombolysis in WUS is comparable to known onset strokes if rtPA given within 4.5 hours of symptoms</td>
</tr>
</tbody>
</table>

aICH=asymptomatic intracerebral hemorrhage; d=day; h=hours; IV=intravenous; mRS=Modified Rankin scale; NECT=Nonenhanced computed tomography; NIHSS=National Institute of Health Stroke Scale; rtPA=recombinant tissue plasminogen activator; sICH=symptomatic intracerebral hemorrhage; WUS=wake up stroke
Wake Up Stroke Current Clinical Trials

Table 6. Wake Up Stroke Current Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Estimated enrollment</th>
<th>Imaging</th>
<th>Primary outcome</th>
<th>Anticipated completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXTEND(^{50})</td>
<td>IV rtPA dosed 0.9 mg/kg within 3-9 hours of onset</td>
<td>400</td>
<td>MRI Penumbral mismatch</td>
<td>mRS at 90d</td>
<td>12/2017</td>
</tr>
<tr>
<td>EXTEND International(^{50}) (NCT01580839)</td>
<td>IV rtPA dosed 0.9 mg/kg within 4.5-9 hours of onset WUS &lt; 9 hours of midpoint</td>
<td>200</td>
<td>CT-CBF or MRI-DWI Penumbral mismatch</td>
<td>mRS at 90d</td>
<td>12/2017</td>
</tr>
<tr>
<td>MR WITNESS(^{51,52}) (NCT01282242)</td>
<td>IV rtPA dosed 0.9 mg/kg within 4.5 hours of discovery LSN within 24 hours</td>
<td>100</td>
<td>MRI DWI-FLAIR</td>
<td>sICH rates</td>
<td>12/2016</td>
</tr>
<tr>
<td>NORT-TEST(^{53}) (NCT01949948)</td>
<td>IV rtPA dosed at 0.9 mg/kg within 4.5 hours of onset or IV tenecteplase 0.4 mg/kg within 4.5 hours of onset</td>
<td>954</td>
<td>MRI</td>
<td>NIHSS at 24h mRS at 90d</td>
<td>01/2017</td>
</tr>
<tr>
<td>SAIL-ON(^{54}) (NCT01643902)</td>
<td>IV rtPA dosed at 0.9 mg/kg within 4.5 hours of onset</td>
<td>20</td>
<td>NECT or MRI DWI-FLAIR</td>
<td>sICH at 36h</td>
<td>12/2014</td>
</tr>
<tr>
<td>THAWS(^{55}) (NCT02002325)</td>
<td>IV rtPA dosed at 0.6 mg/kg within 4.5 hours of onset</td>
<td>300</td>
<td>MRI DWI-FLAIR</td>
<td>mRS at 90d</td>
<td>03/2018</td>
</tr>
<tr>
<td>WAKE-UP(^{56}) (NCT01525290)</td>
<td>IV rtPA dosed 0.9 mg/kg within 4.5 hours of onset</td>
<td>800</td>
<td>MRI DWI-FLAIR</td>
<td>mRS at 90d</td>
<td>12/2016</td>
</tr>
<tr>
<td>WASSABI(^{57}) (NCT01455935)</td>
<td>Active comparator (antiplatelet + statin) or IV rtPA dosed at 0.9 mg/kg or Intra-arterial therapy (rtPA, MERCI device, or PENUMBRA device) within 24 hours of LSN</td>
<td>90</td>
<td>CTP evidence of penumbra</td>
<td>mRS at 90d</td>
<td>02/2014</td>
</tr>
</tbody>
</table>

CBF=cerebral blood flow; CT=computed tomography; CTP=computed tomography perfusion; d=days; DWI=diffusion weighted imaging; FLAIR=fluid-attenuated inversion recovery; h=hours; IV=intravenous; LSN=last seen normal; MRI=magnetic resonance imaging; mRS=modified Rankin score; NECT=non-enhanced computed tomography; rtPA=recombinant tissue plasminogen activator; sICH=symptomatic intracerebral hemorrhage

Conclusions

I. Well-established data shows that supportive care alone does not lead to better outcomes in patients following an ischemic stroke

II. Based on the available literature, treating appropriately selected WUS patients with IV rtPA has not been shown to have worse outcomes when compared to patients with ischemic strokes of known onset times

III. Lack of prospective, randomized controlled trials, limits our ability to determine true safety of rtPA in this patient population

Recommendations

I. Assessment of patients with wake up strokes should be completed emergently as soon as a patient wakes
   a. Patients who wake up with stroke symptoms should be evaluated just as expeditiously as known-onset strokes
   b. I believe we should consider offering rtPA therapy to clinically appropriate patients after the patient (or their medical power of attorney) is made fully aware of the possible risks and benefits of rtPA therapy when rtPA is being administered for this off-label indication

II. Based on the limited data available to date, the following criteria should be met to identify clinical appropriateness
   a. Patient arrives and receives treatment within 4.5 hours after waking with stroke symptoms
   b. NECT shows no changes, or only early ischemic changes
   c. Patient with a mild, moderate, or moderate to severe stroke identified by an NIHSS score < 20
   d. Patient meets all other strict rtPA inclusion/exclusion criteria (minus time restraint) outlined in Appendix C
References


20. The IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischemic stroke (the third international stroke trial [IST-3]): a randomized controlled trial. *Lancet* 2012;379:2352-63.


46. Schwanm LH. “IV alteplase in MR-selected patients with stroke of unknown onset is safe and feasible: results of the multicenter MR WITNESS trial (NCT01282242).” Late-breaking scientific oral abstracts, International Stroke Conference, February 19, 2016, Los Angeles, CA.
### Appendix A. Modified Rankin Scale (mRS) Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms present</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms being present; able to carry out all usual activities and duties</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability present; unable to carry out all previous activities, but able to look after own affairs without any assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requires some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance nor able to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent, and requiring constant nursing attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

### Appendix B. National Institutes of Health Stroke Severity Scale

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
<th>Overall Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a. Level of consciousness (alert, drowsy, etc.)</td>
<td>0= alert 1= drowsy 2= stuporous 3= coma</td>
<td></td>
</tr>
<tr>
<td>1b. Level of consciousness questions (month, age)</td>
<td>0= answers both correctly 1= answers one correctly 2= incorrect</td>
<td></td>
</tr>
<tr>
<td>1c. Level of consciousness commands (open/close eyes, make fist/let go)</td>
<td>0= obeys both correctly 1= obeys one correctly 2= incorrect</td>
<td></td>
</tr>
<tr>
<td>2. Best gaze (eyes open- follows examiner fingers or face)</td>
<td>0= normal 1= partial gaze palsy 2= forced deviation</td>
<td></td>
</tr>
<tr>
<td>3. Visual (visual stimulus/threat to visual field quadrants; cover one eye and hold up fingers in all 4 quadrants)</td>
<td>0= no visual loss 1= partial hemianopsia 2= complete hemianopsia 3= bilateral hemianopsia</td>
<td></td>
</tr>
<tr>
<td>4. Facial palsy (show teeth, squeeze eyes shut, raise eyebrows)</td>
<td>0= normal 1= minor 2= partial 3= complete</td>
<td></td>
</tr>
<tr>
<td>5a. Motor arm- left (elevate limb 90° and score drift/movement; count to 10 out loud, use fingers for visual cue)</td>
<td>0= no drift 1= drift 2= cannot resist gravity 3= no effort against gravity 4= no movement NT= amputation, joint fusion (explain)</td>
<td>Left</td>
</tr>
<tr>
<td>5b. Motor arm- right (elevate limb to 90° and score drift/movement; count to 10 out loud, use fingers for visual cue)</td>
<td>0= no drift 1= drift 2= cannot resist gravity 3= no effort against gravity 4= no movement NT= amputation, joint fusion (explain)</td>
<td>Right</td>
</tr>
<tr>
<td>6a. Motor leg- left (elevate limb to 30° and score drift/movement; count to 5 out loud, use fingers for visual cue)</td>
<td>0= no drift 1= drift 2= cannot resist gravity 3= no effort against gravity 4= no movement NT= amputation, joint fusion (explain)</td>
<td>Left</td>
</tr>
<tr>
<td>6b. Motor leg- right (elevate limb to 30° and score drift/movement; count to 5 out loud, use fingers for visual cue)</td>
<td>0= no drift 1= drift 2= cannot resist gravity 3= no effort against gravity 4= no movement NT= amputation, joint fusion (explain)</td>
<td>Right</td>
</tr>
<tr>
<td>7. Limb ataxia (touch finger to nose; heal down shin)</td>
<td>0= absent 1= present in one limb 2= present in two limbs</td>
<td></td>
</tr>
<tr>
<td>8. Sensory (pin prick to face, arms, trunk, legs; compare sharpness side to side, or no feeling at all)</td>
<td>0= normal 1= partial loss 2= severe loss</td>
<td></td>
</tr>
<tr>
<td>9. Best language (name items, read sentences, describe pictures; ensure patient has glasses prior to this)</td>
<td>0= no aphasia 1= mild to moderate aphasia 2= severe aphasia 3= mute</td>
<td></td>
</tr>
<tr>
<td>10. Dysarthria (evaluate speech clarity; have patient repeat words on a list or read)</td>
<td>0= normal articulation 1= mild to moderate dysarthria 2= near to unintelligible or worse NT= intubated, other physical barrier</td>
<td></td>
</tr>
<tr>
<td>11. Extinction and inattention (use information from previous tests or double simultaneous stimuli testing to identify neglect; visual fields, face, arms, and legs)</td>
<td>0= no neglect 1= partial neglect 2= complete neglect</td>
<td></td>
</tr>
<tr>
<td>NT=not testable</td>
<td>TOTAL SCORE (0 to 42 points)</td>
<td></td>
</tr>
</tbody>
</table>
Appendix C: Stroke Inclusion and Exclusion Criteria for Treatment with rtPA

<table>
<thead>
<tr>
<th>Symptom Onset</th>
<th>Inclusion</th>
<th>Relative Exclusion</th>
<th>Exclusion</th>
</tr>
</thead>
</table>
| < 3 hours     | - Confirmed diagnosis of ischemic stroke  
               - Measurable neurological deficit  
               - Age ≥ 18-years-old  
               - Age > 80-years-old | - Seizure at onset of stroke with postictal residual neurological deficits  
               - Rapidly improving symptoms  
               - Minor stroke symptoms  
               - GI bleed in last 3 weeks  
               - Urinary tract hemorrhage in last 3 weeks  
               - Major surgery or trauma in last 2 weeks  
               - Acute MI in last 3 months  
               - Pregnancy | - Intraspinal or intracranial surgery  
               - SAH symptoms  
               - Previous stroke, head injury, spinal trauma in previous 3 months  
               - Previous ICH  
               - AV malformation, aneurysm, or intracranial neoplasm  
               - Arterial or lumbar puncture in last week  
               - Active internal bleeding  
               - BP >185/110 mmHg refractory to IV treatment  
               - Multilobar infarction (>1/3 cerebral hemisphere hypodensity)  
               - Platelets <100,000 cells/mm³  
               - Use of NOAC or warfarin with INR >1.7 or PT >15 sec  
               - Heparin in last 48 hours with abnormally elevated aPTT > ULN  
               - Direct thrombin inhibitor or direct factor Xa inhibitor with elevated sensitive lab tests  
               - Blood glucose <50 mg/dL or >400 mg/dL | - Intraspinal or intracranial surgery  
               - SAH symptoms  
               - Previous stroke, head injury, spinal trauma in previous 3 months  
               - Previous ICH  
               - AV malformation, aneurysm, or intracranial neoplasm  
               - Arterial or lumbar puncture in last week  
               - Active internal bleeding  
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               - Previous ICH  
               - AV malformation, aneurysm, or intracranial neoplasm  
               - Arterial or lumbar puncture in last week  
               - Active internal bleeding  
               - BP >185/110 mmHg refractory to IV treatment  
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               - Previous stroke, head injury, spinal trauma in previous 3 months  
               - Previous ICH  
               - AV malformation, aneurysm, or intracranial neoplasm  
               - Arterial or lumbar puncture in last week  
               - Active internal bleeding  
               - BP >185/110 mmHg refractory to IV treatment  
               - Multilobar infarction (>1/3 cerebral hemisphere hypodensity)  
               - Platelets <100,000 cells/mm³  
               - Use of NOAC or warfarin with INR >1.7 or PT >15 sec  
               - Heparin in last 48 hours with abnormally elevated aPTT > ULN  
               - Direct thrombin inhibitor or direct factor Xa inhibitor with elevated sensitive lab tests  
               - Blood glucose <50 mg/dL or >400 mg/dL |

aPTT=activated partial thromboplastin time; AV=arteriovenous; BP=blood pressure; GI=gastrointestinal; ICH=intracranial hemorrhage; INR=international normalized ratio; IV=intravenous; MI=myocardial infarction; NIHSS=National Institutes of Health Stroke Scale; NOAC=novel oral anticoagulant; rtPA=recombinant tissue plasminogen activator; PT=prothrombin time; SAH=subarachnoid hemorrhage; ULN=upper limit of normal