Acute Ischemic Stroke
Mechanism, Diagnosis, Treatment

IM Resident Lecture
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Objectives

• Better understanding of stroke mechanisms contributing to stroke etiology
• Develop a systematic diagnostic approach that will facilitate expeditious identification of patients eligible for acute therapies.
• Familiarity with current selection criteria for acute stroke reperfusion therapies
Mechanism of Brain Tissue Injury in Stroke

Stroke: Acute injury to brain by an abnormality of blood supply

**Ischemic Stroke**

~ 80%

Lack of or diminished blood flow

**Hemorrhagic Stroke**

~20%

Release of blood into the brain & extravascular spaces within the cranium or skull
Acute Reperfusion Therapy

• Treatment intended to emergently restoring blood flow in the acutely occluded cerebral artery.
  – Pharmacologic – IV tPA, and/or
  – Mechanical – Endovascular mechanical thrombectomy
The Numbers

- **Nationally**
  - ~800,000 new annual stroke cases with ~600,000 first-time strokes
  - *Fifth* cause of death with ~130,000 stroke-related deaths per year
  - On average,
    - every 40 seconds, someone has a stroke
    - every 4 minutes, someone died of a stroke
  - Women have a higher lifetime risk of stroke than men
    - Affects 3 times as many women as breast CA and receives much less public attention
  - Stroke morbidity and mortality disproportionately affects minority populations
  - Between 2012 and 2030 the total direct medical stroke-related costs are projected to triple, from $71.6 to $184.1 billion

- **Globally**
  - In 2013, *second*-leading cause of death (after heart disease)
  - In 2010, 33 million strokes with 16.9 million as a first stroke
  - Burden of stroke now disproportionately affects those living in lower-income countries

- **Both globally and nationally**
  - A leading cause of disability

Mozzafarrian et al. 2016
Cerebrovascular Arterial Circulation
Cerebrovascular Arterial Circulation: Large Vessels

Anterior Circulation

Posterior Circulation
Cerebrovascular Arterial Circulation: Small Vessels—Penetrators/Perforators

Anterior Circulation

Lateral lenticulostriate arteries
Medial lenticulostriate arteries
Middle cerebral artery
Anterior cerebral artery
Recurrent artery (of Heubner)
Internal carotid artery
Anterior communicating artery

Posterior Circulation

Midbrain
Pons
Medulla

Right PCA
Post communicating artery
A1
PCoA
Thalamogeniculate artery
Left PCA

A
B
C

UC Irvine Health
Ischemic Stroke Mechanisms

• A heterogeneous disease
  – Classification is not always straight-forward
  – Potential for combination of mechanisms

• Thrombosis

• Embolism

• Hypoperfusion
Ischemic Stroke Mechanisms

**Thrombosis**

- Localized obstruction of blood flow due to an occlusive process with one or more blood vessels
  - Atherosclerosis, most common vascular pathology
    - Larger extra- and intra-cranial arteries
    - Areas of turbulent flow and low shear stress, i.e. arterial bifurcations
  - Hypertension
    - Hypertrophy of media ➔ Lipohyalinosis
    - Small intracranial penetrating and perforating arteries
  - Dissection
  - Primary hematologic conditions
  - Arteritis/Vasculitis
Ischemic Stroke Mechanisms

**Embolism**

- Material formed elsewhere, typically from a proximal donor source, within the vascular system lodges in a recipient artery and blocks blood flow
  - Cardiac source, most common
  - Major arteries - artery-to-artery embolism
  - Paradoxical embolism from systemic veins
    - Through venous to arterial shunts, i.e. PFO, ASD
  - Cholesterol (post-fracture), air, fibrocartilagenous tissue, amniotic fluid, tumor
Ischemic Stroke Mechanisms

**Hypoperfusion**

- \( \downarrow \) systemic perfusion \( = \) \( \downarrow \) cerebral perfusion
- “watershed” regions most susceptible at periphery of major vascular supply territory
  - Cardiac, most common
  - Blood loss,
  - Hypovolemia
Ischemic Stroke Subtypes

• TOAST classification of subtypes of acute ischemic stroke (Adams et al. 1993)
  – Classification scheme for ischemic stroke widely used with good inter-observer agreement
  – Attempts to classify based on the major mechanisms recognized as the cause of most ischemic strokes
  – Five subtypes
    • Large artery disease (20%) – highest recurrence
    • Small vessel disease (25%) – best outcomes, survival, recurrence
      – Lacunar:
    • Cardioembolic (20%) – worst outcomes, highest mortality
    • Stroke of other determined etiology (5%)
    • Cryptogenic (30%)
Transient Ischemic Attack (TIA)

• “A brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than an hour, and without evidence of acute infarction.”

• Transient reduction of blood flow to a region in brain in the absence of infarction on brain imaging

• Most TIAs last only a few minutes and the great majority less than an hour.
  • Those lasting longer than an hour often associated with brain infarction on MRI DWI
Transient Ischemic Attack (TIA)

- Mechanisms for TIA are similar to ischemic stroke

- Reconstitution of flow to the hypoperfused region results in the resolution of symptoms

- Significance of TIAs is increased risk of ischemic stroke after a TIA specifically early on after a TIA

- Prompt evaluation of mechanism and appropriate treatment
## ABCD² Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 60 years</td>
<td>1</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td></td>
</tr>
<tr>
<td>Systolic BP ≥ 140 mmHg OR Diastolic BP ≥ 90 mmHg</td>
<td>1</td>
</tr>
<tr>
<td><strong>Clinical features of TIA</strong></td>
<td></td>
</tr>
<tr>
<td>Unilateral weakness w/ or w/o speech impairment OR Speech impairment w/o unilateral weakness</td>
<td>2</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 60 minutes</td>
<td>2</td>
</tr>
<tr>
<td>10-59 minutes</td>
<td>1</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Total ABCD² score</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-7</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td></td>
</tr>
<tr>
<td>0-3: 1.0% 2-day stroke risk</td>
<td></td>
</tr>
<tr>
<td>4-5: 4.1% 2-day stroke risk</td>
<td></td>
</tr>
<tr>
<td>6-7: 8.1% 2-day stroke risk</td>
<td></td>
</tr>
</tbody>
</table>
Approach To Guide Acute Reperfusion Therapy

• Goal: Expeditious identification of eligible patients
  – Bedside history and exam
  – Neuroimaging
  – Ancillary Testing
History

• Time
  – Symptom onset-time available
    • Use of cues
  – Last well-known time (LKWT)
  – Awaken with symptoms
  – Reset after TIA

• Nature of symptom onset
  – Sudden and maximal: embolic
  – Gradual and progressive: thrombotic

• Other significant medical history
History

- History of the present illness
  - Time of symptom onset
  - Evolution of symptoms
  - Convulsion or loss of consciousness at onset
  - Headache
  - Chest pain at onset

- Medical history
  - Prior intracerebral hemorrhage
  - Recent stroke
  - Recent head trauma or loss of consciousness
  - Recent myocardial infarction

- Surgical History
  - Recent surgical procedures
  - Arterial puncture

- Review of systems
  - Gastrointestinal or genitourinary bleeding

- Medications
  - Anticoagulant therapy
# Common Ischemic Stroke Syndromes

<table>
<thead>
<tr>
<th>Vascular Territory</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>L MCA distribution</td>
<td>Aphasia, R hemiparesis/hemisensory disturbance, R homonymous hemianopsia, L head and gaze preference</td>
</tr>
<tr>
<td>R MCA distribution</td>
<td>L hemispatial neglect, L hemiparesis/hemisensory disturbance, L homonymous hemianopsia, R head and gaze preference, anosognosia</td>
</tr>
<tr>
<td>L PCA distribution</td>
<td>R visual field defect, impaired reading with intact writing (alexia without agraphia), poor color naming, R hemisensory disturbance</td>
</tr>
<tr>
<td>R PCA distribution</td>
<td>L visual field defect, visual neglect, L hemisensory disturbance</td>
</tr>
<tr>
<td>Vertebrobasilar distribution</td>
<td>Dizziness, vertigo, nausea, diplopia, quadriplegia, crossed motor or sensory findings, truncal or limb ataxia, visual loss/dimming, impaired consciousness</td>
</tr>
</tbody>
</table>

**Penetrating artery distribution (ie, lacunar syndromes)**

| (A) Internal capsule/corona radiata | (A, B) Contralateral hemiparesis alone (pure motor stroke) OR contralateral hemiparesis + ataxia out of proportion to weakness (ataxic-hemiparesis); no cortical signs |
| (B) Ventral pons                    |                                                                                       |
| (C) Thalamus                        | (C) Contralateral sensory loss alone (pure sensory stroke); no cortical sign            |
## Neurologic Examination: The NIH Stroke Scale (NIHSS)

<table>
<thead>
<tr>
<th>Category</th>
<th>Scale Definition</th>
<th>Category</th>
<th>Scale Definition</th>
<th>Category</th>
<th>Scale Definition</th>
</tr>
</thead>
</table>
| 1a. LOC  | 0 = Alert  
1 = Not alert, arousable  
2 = Not alert, obtunded  
3 = Unresponsive | 5a. L motor arm | 0 = No drift  
1 = Drift before 10 seconds  
2 = Falls before 10 seconds  
3 = No effort against gravity  
4 = No movement | 7. Ataxia | 0 = Absent  
1 = One limb  
2 = Two limbs |
| 1b. Questions | 0 = Answers both correctly  
1 = Answers one correctly  
2 = Answers neither correctly | 5b. R motor arm | 0 = No drift  
1 = Drift before 10 seconds  
2 = Falls before 10 seconds  
3 = No effort against gravity  
4 = No movement | 8. Sensory | 0 = Normal  
1 = Mild loss  
2 = Severe loss |
| 1c. Commands | 0 = Performs both tasks correctly  
1 = Performs one task correctly  
2 = Performs neither task | 6a. L motor leg | 0 = No drift  
1 = Drift before 10 seconds  
2 = Falls before 10 seconds  
3 = No effort against gravity  
4 = No movement | 9. Language | 0 = Normal  
1 = Mild aphasia  
2 = Severe aphasia  
3 = Mute or global aphasia |
| 2. Gaze | 0 = Normal  
1 = Partial gaze palsy  
2 = Total gaze palsy | 6b. R motor leg | 0 = No drift  
1 = Drift before 10 seconds  
2 = Falls before 10 seconds  
3 = No effort against gravity  
4 = No movement | 10. Dysarthria | 0 = Normal  
1 = Mild  
2 = Severe |
| 3. Visual fields | 0 = No visual loss  
1 = Partial gaze palsy  
2 = Total gaze palsy | | | 11. Extinction/inattention | 0 = Normal  
1 = Mild  
2 = Severe |
| 4. Facial Palsy | 0 = Normal  
1 = Minor paralysis  
2 = Partial paralysis  
3 = Complete paralysis | | | | |
Neurologic Examination: The NIH Stroke Scale (NIHSS)

• Limitation of NIHSS
  – Does not include a detailed assessment of CNs
  – Milder deficits may escape detection
  – Higher stroke severity in dominant vs non-dominant hemispheres

• NIHSS should not take the place of a focused and thorough neurologic evaluation
## Differential Diagnosis

### Intracerebral hemorrhage vs Stroke mimics

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure (Post-ictal)</td>
<td>Focal deficits. Spontaneous resolution over hours (may last up to 48 hours)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Aphasia or hemiplegia. Variable drowsiness or obtundation. Blood glucose usually &lt;45 mg/dL. Resolution of symptoms (immediate to hours) with IV glucose.</td>
</tr>
<tr>
<td>Migraine</td>
<td>Symptoms begin in one region and gradually spread to involve other areas.</td>
</tr>
<tr>
<td>Mass lesions/Tumor</td>
<td>Duration of symptoms. Associated symptoms.</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>Headache, thunderclap headache.</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Hypertensive, hyperosmolar hyperglycemia, hyponatremia, hepatic. Associated with altered LOC, poor attention, or disorientation</td>
</tr>
<tr>
<td>Peripheral vestibulopathy</td>
<td>Vertigo, nystagmus on exam, nausea, emesis.</td>
</tr>
<tr>
<td>Reactivation of prior deficits</td>
<td>Imaging evidence or history of remove stroke. Previous deficits may have resolved completely.</td>
</tr>
<tr>
<td>Conversion reaction</td>
<td>Diagnosis of exclusion. Comorbid psychiatric problems are common. Paresis, paralysis, and movement disorders are common.</td>
</tr>
</tbody>
</table>
Acute Stroke Neuroimaging

• Initial imaging of brain parenchyma
  – Exclude hemorrhagic stroke: CT or MRI

Ischemia

Hemorrhage
Acute Stroke Neuroimaging

- For acute hemorrhage accuracy of MRI (GRE sequences) is equal to that of CT. (Kidwell et al, 2004)
Acute Stroke Neuroimaging
CT vs MRI

• CT
  • Advantages: Fast acquisition time, widely available, sensitive to hemorrhage
  • Disadvantages: Limited sensitivity to infarct size, location of early ischemia

• MRI (DWI sequence)
  • Advantage: Sensitive to early ischemia, fast acquisition time, high conspicuity of lesion
  • Disadvantage: Lack of availability, patient contraindication (eg, metals, claustrophobia), long acquisition time
Acute Stroke Neuroimaging

• Imaging of the early ischemic changes: CT or MRI

• Non-contrast CT (within 6-8 hour)
  – Specificity: 56-100%
  – Sensitivity: 20-75%
  – Worse in posterior fossa ischemia

• MRI DWI sequence (within <6 hours)
  – Specificity: 86-100%
  – Sensitivity: 91-100%
Multimodal Neuroimaging

- Potential to improve patient selection criteria to guide therapy

- Noninvasive multimodal CT and MR
  - Angiography (A): vessel imaging (CTA, MRA)
  - Perfusion (P): tissue viability, cerebral perfusion (CTP, MRP)

- Multimodal MRI parenchymal sequences
  - Diffusion-weighted imaging (DWI)
  - Apparent diffusion coefficient (ADC)
  - Fluid-attenuated inversion recovery (FLAIR)
  - Gradient recoiled echo (GRE)
  - Susceptibility-weighted imaging (SWI)

- No standardized imaging protocols for acute stroke exist

- Advanced neuroimaging should not delay the administration of IV rtPA
Ancillary Testing

- Blood glucose (Finger stick is acceptable)
  - The only lab result needed for administration of IV tPA

- Administration of IV tPA should NOT be delayed while awaiting results of the following lab results:
  - Complete blood count (CBC)
    - Unless clinical suspicion of a bleeding abnormality or thrombocytopenia
    - < 3/1000 will have unsuspected thrombocytopenia (Cucchiara et al, 2007)
  - Coagulation panel (PT/INR/PTT)
    - Patient has received heparin or warfarin,
    - Patient has received other anticoagulants
    - <4/1000 will have an unsuspected INR>1.7 (Rost et al, 2009)
  - Chemistry panel (Chem7)
  - Cardiac enzymes
  - CXR
  - 12-lead ECG
Acute Ischemic Stroke Therapy

- **Neuroprotectants**
  - Over 1,000 agents in clinical trials
  - None has proved successful

- **Acute reperfusion therapy**
  - IV rtPA (tissue plasminogen activator)
  - Endovascular thrombectomy/embolectomy
  - Combination of above

- **Treatment is time-dependent**
  - Time is Brain!!
Recombinant Tissue Plasminogen Activator (rtPA)

- The only FDA-approved thrombolytic agent
  - Up to 3 hours from symptom onset time

- Recommended by AHA/ASA
  - Up to 4.5 hours from symptom onset time
  - Selected patient population
  - NOT FDA-approved

- Other agents available as experimental in the context of clinical trials
  - Desmoteplase, Tenecteplase
### Recombinant Tissue Plasminogen Activator (rtPA)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Dose</th>
<th>Time of outcome assessment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom onset: 0–3 h</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haley et al.</td>
<td>1993</td>
<td>27</td>
<td>0.85 mg/kg</td>
<td>3 months</td>
<td>NIHSS</td>
</tr>
<tr>
<td>NINDS I</td>
<td>1995</td>
<td>291</td>
<td>0.9 mg/kg (max. 90 mg)</td>
<td>24 h</td>
<td>NIHSS</td>
</tr>
<tr>
<td>NINDS II (Pivotal)</td>
<td>1995</td>
<td>333</td>
<td>0.9 mg/kg (max. 90 mg)</td>
<td>3 months</td>
<td>NIHSS, GOS, BI, mRS</td>
</tr>
<tr>
<td>NINDS I and II</td>
<td>1995</td>
<td>624</td>
<td>0.9 mg/kg (max. 90 mg)</td>
<td>3 months</td>
<td>NIHSS, GOS, BI, mRS</td>
</tr>
<tr>
<td><strong>Symptom onset: 0–6 h</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mori et al.</td>
<td>1992</td>
<td>34</td>
<td>0.6 mg/kg vs. 0.9 mg/kg</td>
<td>1 month</td>
<td>Reperfusion (A), HSS</td>
</tr>
<tr>
<td>JTSG</td>
<td>1993</td>
<td>98</td>
<td>0.6 mg/kg (34 mg)</td>
<td>1 month</td>
<td>Reperfusion (A), HSS</td>
</tr>
<tr>
<td>ECASS</td>
<td>1995</td>
<td>620</td>
<td>1.1 mg/kg (max. 100 mg)</td>
<td>3 months</td>
<td>mRS, BI</td>
</tr>
<tr>
<td>ECASS II</td>
<td>1998</td>
<td>800</td>
<td>0.9 mg/kg (max. 90 mg)</td>
<td>3 months</td>
<td>mRS 2–6</td>
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<tr>
<td>ATLANTIS A</td>
<td>2000a</td>
<td>142</td>
<td>0.9 mg/kg (max. 90 mg)</td>
<td>3 months</td>
<td>mRS 2–6, BI, NIHSS</td>
</tr>
<tr>
<td>ATLANTIS B</td>
<td>1999a</td>
<td>613</td>
<td>0.9 mg/kg (max. 90 mg)</td>
<td>3 months</td>
<td>mRS 2–6, BI, NIHSS</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>2003</td>
<td>100</td>
<td>0.9 mg/kg (max. 90 mg)</td>
<td>3 months</td>
<td>CSS, BI</td>
</tr>
<tr>
<td>IST-3</td>
<td>2012</td>
<td>3,035</td>
<td>0.9 mg/kg (max. 90 mg)</td>
<td>6 months</td>
<td>OHS 0–2</td>
</tr>
<tr>
<td><strong>Symptom onset: 3–4.5 h</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECASS III</td>
<td>2008</td>
<td>821</td>
<td>0.9 mg/kg (max. 90 mg)</td>
<td>3 months</td>
<td>mRS 0–1</td>
</tr>
<tr>
<td><strong>Symptom onset: 3–6 h</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPITHET</td>
<td>2008</td>
<td>101</td>
<td>0.9 mg/kg (max. 90 mg)</td>
<td>3 months</td>
<td>Infarct Growth</td>
</tr>
</tbody>
</table>

**RCTs of rtPA for Acute Ischemic Stroke**
NINDS Stroke Study

• Clinical question:
  – In patients with ischemic stroke presenting within 3 hours of symptom onset does the administration of rtPA reduce morbidity and mortality?

• Multicenter, double-blinded, randomized, placebo-controlled trial

• N=624
  – Exclusion mostly based on risk of bleeding
  – No exclusion based on severity of stroke or maximum age
• Divided in 2 parts
  – Part 1: Improvement by >4 points on NIHSS or complete resolution at 24 hours
    • 47% vs 39% (RR 1.2; 95% CI 0.9-1.6; p=0.21)
  – Part 2: Proportion after stroke with favorable outcomes at 90 days
    • Barthel Index: 50% vs 38% (OR 1.6; 95% CI 1.1-2.5, p=0.026)
    • Modified Rankin Scale: 39% vs 26% (OR 1.7; 95% CI 1.1-2.6, p=0.019)
    • Glasgow outcome scale: 44% vs 32% (OR 1.6; 95% CI 1.1-2.5, p=0.025)
    • NIHSS: 31% vs 20% (OR 1.7; 95% CI 1.0-2.8; p=0.033)
    – 90-day Mortality: 17% vs 21% (p=0.30)

• Adverse Events: ICH within 36 hours of stroke treatment
  – 6.4% vs 0.6% (p<0.001), of which 45% were fatal

• NNT to prevent significant disability: 8
ECASS III

• Clinical question:
  – In patients with ischemic stroke presenting up to 4.5 hours of symptom onset does the administration of rtPA reduce disability?

• Multicenter, double-blinded, randomized, placebo-controlled trial
  – N=821; follow up of 3 months
  – Exclusion mostly based on risk of bleeding
  – Exclusion of patients
    • > 80 yo
    • NIHSS score > 25
    • Prior stroke AND diabetes
    • Warfarin (regardless of INR)
ECASS III continued

- **Primary Outcome**: 90-day disability (mRS of 0 or 1)
  - 52.4% vs 45.2% (OR 1.34; 95% CI 1.02-1.76; p=0.04)

- **Secondary Outcome**: Global outcome
  - Favoring rtPA: (OR 1.28; 95% CI 1.00-1.65, p<0.05)
  - Barthel Index: 63.4% vs 58.6% (OR 1.23; 95% CI 0.93-1.62, p=0.16)
  - Glasgow outcome scale: 51.0% vs 45.4% (OR 1.25; 95% CI 0.95-1.64, p=0.11)
  - NIHSS: 50.2% vs 43.2% (OR 1.33; 95% CI 1.01-1.75; p=0.04)

- **NNT for a favorable outcome**: 13.8

- **Adverse Events**
  - Any ICH: 27.0% vs 17.6%
  - Symptomatic ICH:
    - ECASS III definition: 2.4% vs 0.2% (OR 9.85; 95% CI 1.26-77.32; p=0.008; NNH=45)
    - NINDS definition: 7.9% vs 3.5% (OR 2.38; 95% CI 1.25-4.52; p=0.006; NNH=23)

- **90-day Mortality**
  - 7.7% vs 8.4% (OR 0.80; 95% CI 0.54-1.49; p=0.68)
Time is Brain

- Every minute in which a large vessel ischemic stroke is untreated, the average patient loses
  - 1.9 million neurons,
  - 13.8 billion synapses,
  - 12 km (7 miles) of axonal fibers.
- Each hour in which treatment fails to occur, the brain loses as many neuron as it does in almost 3.6 years of normal aging.
Time is Brain
Faster Treatment = Better Outcomes

- The greatest population benefit would occur by treating more patients early.
### Table 3. Binary Clinical Outcomes in Patients With Documented National Institutes of Health Stroke Scale Scores With Onset-to-Treatment Times 0 to 90, 91 to 180, and 181 to 270 Minutes (n = 51,158)

<table>
<thead>
<tr>
<th>Outcome, No. of Patients (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-90</td>
<td>91-180</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=4813</td>
<td>373</td>
<td>3425</td>
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<tr>
<td>P value</td>
<td>.58</td>
<td>.06</td>
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<tr>
<td>ITPA complications</td>
<td></td>
<td></td>
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<tr>
<td>n=4813</td>
<td>463</td>
<td>4160</td>
</tr>
<tr>
<td>P value</td>
<td>.01</td>
<td>.08</td>
</tr>
<tr>
<td>Symptomatic intracranial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=4813</td>
<td>193</td>
<td>1965</td>
</tr>
<tr>
<td>P value</td>
<td>.004</td>
<td>.01</td>
</tr>
<tr>
<td>Serious systemic hemorrhage</td>
<td></td>
<td></td>
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<tr>
<td>n=4813</td>
<td>40</td>
<td>432</td>
</tr>
<tr>
<td>P value</td>
<td>.17</td>
<td>.10</td>
</tr>
<tr>
<td>Ambulation independent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at discharge</td>
<td>1706</td>
<td>13132</td>
</tr>
<tr>
<td>P value</td>
<td>.77</td>
<td>.05</td>
</tr>
<tr>
<td>Discharge home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=4813</td>
<td>1928</td>
<td>15072</td>
</tr>
<tr>
<td>P value</td>
<td>.005</td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; OTT, onset to treatment; ITPA, tissue-type plasminogen activator.
BOX 1-1  IV rtPA Exclusion and Relative Contraindication Criteria

Key IV rtPA Exclusion Criteria

- Stroke or significant head trauma within 3 months
- Major surgery or serious trauma within 14 days
- Gastrointestinal or urinary hemorrhage within 21 days
- Arterial puncture at a noncompressible site within 7 days
- History of intracranial hemorrhage
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
  - Some experts consider treating patients with remotely secured or unruptured aneurysms
- Symptoms of subarachnoid hemorrhage
- Active internal bleeding
- Pretreatment blood pressure with systolic >185 mm Hg or diastolic >110 mm Hg
- Clear and large hypodensity on CT scan
- Current bleeding diathesis including
  - International normalized ratio (INR) >1.7
  - Heparin within 48 hours resulting in abnormal partial thromboplastin time (PTT)
  - Platelets <100,000/mm³
  - Direct thrombin inhibitor (eg, dabigatran) or factor Xa inhibitor (eg, rivaroxaban, apixaban) use within 48 hours
    - Optimal laboratory testing thresholds for safe IV recombinant tissue-type plasminogen activator (rtPA) use in this setting remain to be determined and are an area of active investigation.
- Serum glucose <50
  - If persistent symptoms after correction, or infarct is verified/supported by imaging, most experts would consider IV rtPA treatment.

Relative Contraindications for IV rtPA

- Minor deficit
  - Rapidly improving deficits should not be considered a contraindication unless the remaining deficit is minor.²³
  - A common definition of minor deficits is an NIH Stroke Scale (NIHSS) score ≤5 and not clearly disabling.
  - A consensus definition of deficits that should typically be considered disabling (regardless of total NIHSS score) is shown in Table 1-1.
- Myocardial infarction in the past 3 months
  - Some experienced centers treat this as a contraindication only if the myocardial infarction is subacute and transmural, or other signs suggest a high risk of hemothorax, such as clinical or ECG evidence of pericarditis.
  - Concurrent acute myocardial infarction may benefit from IV rtPA as well and should be entertained.

Additional Exclusion Criteria for IV rtPA Within the 3- to 4.5-Hour Time Window

- History of stroke AND diabetes mellitus
- NIHSS score >25
- Age >80 years old
- On warfarin (regardless of INR value)
## AHA/ASA Scientific Statement

### Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

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<td>Bleeding diathesis remains a contraindication, but all laboratory values and specific examples removed</td>
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</table>
Treatment Timeline Goals

• IV tPA within 60 minutes of arrival to an ED
  – Evaluation by ED physician (10 minutes)
  – Evaluation by stroke/neurologist (15 minutes)
  – Non-contrast CT scan is completed (25 minutes)
  – CT is interpreted (45 minutes)
• Faster treatment = Better outcomes
Post-Reperfusion Therapy

• Standard post-tPA management for the first 24 hours:
  – Admission to Stroke Unit ICU level of care
  – NPO until dysphagia screening to avoid aspiration PNA
  – Isotonic IV fluids (not dextrose containing because of risk of hyperglycemia)
  – BP and neurologic monitoring
    • Q15min x 2 hrs, then
    • Q30min x 6 hrs, then
    • Q60min x 16 hrs
  – Aggressive BP treatment
    • If SBP>180 mmHg or DBP >105 mmHg
  – Emergent CT scan if neurologic decline, acute increase in BP, N/V, new HA
  – Repeat brain imaging at 24 hours to assess for asymptomatic hemorrhage
Endovascular Therapies

- Five positive endovascular RCTs for treatment of acute ischemic stroke:

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Country; Year</th>
<th>Number of Patients Enrolled</th>
<th>Time Window (Symptom Onset to Groin Puncture)</th>
<th>Parenchymal Imaging Selection</th>
<th>Vascular Imaging Selection</th>
<th>Recanalization (TICI 2b/3)</th>
<th>Minutes to Reperfusion (Range)</th>
<th>Reperfusion at 24 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)</td>
<td>Netherlands; 2010-2014</td>
<td>N = 500</td>
<td>6 hours</td>
<td>NCT</td>
<td>CTA/MRA/DSA</td>
<td>58.7%</td>
<td>332 (275-394)</td>
<td>75.4% versus 32.9%</td>
</tr>
<tr>
<td>Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE)</td>
<td>Canada, United States, South Korea, Ireland, United Kingdom; 2013-2014</td>
<td>N = 316</td>
<td>12 hours</td>
<td>NCT (ASPECTS ≥6)</td>
<td>Multiphase CTA (collateral filling of ≥50% of middle cerebral artery-pia)</td>
<td>72.4%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial (EXTEND IA)</td>
<td>Australia, New Zealand; 2012-2014</td>
<td>N = 70</td>
<td>6 hours (90 minutes from image to groin puncture)</td>
<td>CT/MR diffusion-perfusion; Tmax &gt;6-second delay perfusion volume and rCBF or DWI for ischemic core (using RAPID software); Included mismatch ratio &gt;1.2, absolute mismatch volume &gt;10 ml, ischemic core &lt;70 ml</td>
<td>CTA/MRA</td>
<td>86.0%</td>
<td>248 (204-277)</td>
<td>89% versus 34%</td>
</tr>
<tr>
<td>Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment Trial (SWIFT PRIME)</td>
<td>United States; 2012-2014</td>
<td>N = 197</td>
<td>6 hours (90 minutes from image to groin puncture)</td>
<td>NCT (ASPECTS ≥7) CT/MR diffusion-perfusion; Tmax &gt;10-second delay perfusion volume and rCBF or DWI for ischemic core (RAPID); Included mismatch ratio &gt;1.8, absolute mismatch volume ≥15 ml, ischemic core ≤50 ml</td>
<td>CTA/MRA</td>
<td>88.0%</td>
<td>Not reported</td>
<td>Reperfusion at 27 hours; 83% versus 40%</td>
</tr>
<tr>
<td>Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptoms Onset (REVASCAT)</td>
<td>Spain; 2012-2014</td>
<td>N = 206</td>
<td>8 hours</td>
<td>NCT (ASPECTS ≥7)</td>
<td>CTA/MRA</td>
<td>66.0%</td>
<td>355 (269-430)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
AHA/ASA Guideline

2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association
Endovascular Interventions

• Patients eligible for intravenous r-tPA should receive intravenous r-tPA even if endovascular treatments are being considered (Class I; Level of Evidence A).

• Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria (Class I; Level of Evidence A). (New recommendation):
  – Prestroke mRS score 0 to 1,
  – Acute ischemic stroke receiving intravenous r-tPA within 4.5 hours of onset according to guidelines from professional medical societies,
  – Causative occlusion of the ICA or proximal MCA (M1),
  – Age ≥18 years,
  – NIHSS score of ≥6,
  – ASPECTS of ≥6, and
  – Treatment can be initiated (groin puncture) within 6 hours of symptom onset

• In carefully selected patients with anterior circulation occlusion who have contraindications to intravenous r-tPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable (class IIA; level of evidence C). (New recommendation)
Imaging

• **Emergency imaging of the brain** is recommended **before any specific treatment** for acute stroke is initiated (Class I; Level of Evidence A). In most instances, nonenhanced CT will provide the necessary information to make decisions about emergency management.

• If endovascular therapy is contemplated, a **noninvasive intracranial vascular study** is strongly recommended during the **initial imaging evaluation** of the acute stroke patient but **should not delay intravenous r-tPA** if indicated. For patients who qualify for intravenous r-tPA according to guidelines from professional medical societies, initiating intravenous r-tPA before noninvasive vascular imaging is recommended for patients who have not had noninvasive vascular imaging as part of their initial imaging assessment for stroke. Noninvasive intracranial vascular imaging should then be obtained as quickly as possible (Class I; Level of Evidence A). (New recommendation)

• The **benefits of additional imaging** beyond CT and CTA or MRI and MRA such as CT perfusion or diffusion- and perfusion-weighted imaging for selecting patients for endovascular therapy are **unknown** (Class IIb; Level of Evidence C). (New recommendation)
Summary

• A leading cause of disability and death both in the US and globally

• Acute stroke treatment requires emergent and streamlined evaluation in a certified stroke center

• IV tPA is considered standard of care

• Endovascular treatment with mechanical thrombectomy has also become a standard of care for selected patients
Questions??
### Neurologic Examination:

**The NIH Stroke Scale (NIHSS)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Scale Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a. LOC</td>
<td>0 = Alert, 1 = Not alert, arousable, 2 = Not alert, obtunded, 3 = Unresponsive</td>
</tr>
<tr>
<td>1b. Questions</td>
<td>0 = Answers both correctly, 1 = Answers one correctly, 2 = Answers neither correctly</td>
</tr>
<tr>
<td>1c. Commands</td>
<td>0 = Performs both tasks correctly, 1 = Performs one task correctly, 2 = Performs neither task</td>
</tr>
<tr>
<td>2. Gaze</td>
<td>0 = Normal, 1 = Partial gaze palsy, 2 = Total gaze palsy</td>
</tr>
<tr>
<td>3. Visual fields</td>
<td>0 = No visual loss, 1 = Partial gaze palsy, 2 = Total gaze palsy</td>
</tr>
<tr>
<td>4. Facial Palsy</td>
<td>0 = Normal, 1 = Minor paralysis, 2 = Partial paralysis</td>
</tr>
</tbody>
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## Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke

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</tr>
<tr>
<td>Bleeding diathesis/OACs</td>
<td>Exclusion: Platelet count &lt;100 000/mm³, Heparin received within 48 h, resulting in abnormally elevated aPTT. Current use of anticoagulant with INR &gt;1.7 or PT &gt;15 s. Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests.</td>
<td>Contraindication: known bleeding diathesis including but not limited to: Current use of OACs (e.g., warfarin sodium), an INR &gt;1.7, or a PT &gt;15 s. Administration of heparin within 48 h preceding the onset of stroke with an elevated aPTT at presentation. Platelet count &lt;100 000/mm³. Warning for all indications: patients currently taking OACs.</td>
<td>Bleeding diathesis remains a contraindication, but all laboratory values and specific examples removed.</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------------------------------</td>
<td>----------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>ICH</td>
<td>Exclusion: history of previous ICH</td>
<td>Contraindication: history of ICH</td>
<td>Contraindication removed Warning added for recent ICH</td>
</tr>
<tr>
<td>BP</td>
<td>Exclusion: Elevated BP (systolic &gt;85 mm Hg or diastolic &gt;10 mm Hg)</td>
<td>Contraindication: uncontrolled hypertension at the time of treatment (eg, &gt;185 mm Hg systolic or &gt;110 mm Hg diastolic)</td>
<td>Contraindication: current severe uncontrolled hypertension remains, specific BP values removed Warning for BP &gt;175/110 mm Hg remains for all alteplase indications</td>
</tr>
<tr>
<td>--------------------</td>
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<td>----------------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Blood glucose</td>
<td>Exclusion: blood glucose &lt;50 mg/dL</td>
<td>Warning: because of the increased risk for misdiagnosis of acute ischemic stroke, special diligence is required in making this diagnosis in patients whose blood glucose values are ≈50 or &gt;400 mg/dL</td>
<td>Removed entirely</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Severe stroke</td>
<td>Not listed</td>
<td>Warning: patients with severe neurological deficit (NIHSS score &gt;22) at presentation; there is an increased risk of ICH in these patients</td>
<td>Removed entirely</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Mild stroke</td>
<td>Relative exclusion: only minor or rapidly improving stroke symptoms (clearing spontaneously)</td>
<td>Warning: safety and efficacy in patients with minor neurological deficit or with rapidly improving symptoms have not been evaluated; therefore, treatment of patients with minor neurological deficit or with rapidly improving symptoms is not recommended</td>
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<tr>
<td>Neuroimaging findings</td>
<td>Exclusion: CT demonstrates multilobar infarction (hypodensity &gt;1/3 cerebral hemisphere)</td>
<td>Warning: Major early infarct sign (substantial edema, mass effect, or midline shift on CT)</td>
<td>Removed entirely</td>
</tr>
<tr>
<td>SAH</td>
<td>Exclusion: symptoms suggest SAH</td>
<td>Contraindication: Suspicion of SAH on pretreatment evaluation</td>
<td>Contraindication: subarachnoid hemorrhage</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Use in specific populations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Relative exclusion</td>
<td>Warning: pregnancy Category C</td>
<td>No change</td>
</tr>
<tr>
<td>Nursing mothers</td>
<td>Not listed</td>
<td>Not mentioned</td>
<td>Unknown risk</td>
</tr>
<tr>
<td>Children</td>
<td>Inclusion: ≥18 y of age</td>
<td>Indicated for adults</td>
<td>Pediatric use not established</td>
</tr>
<tr>
<td>Elderly</td>
<td>Not listed</td>
<td>Warning for all indications: advanced age (eg, &gt;75 y) may increase risks</td>
<td>Warning added: age &gt;77 y was 1 of several interrelated baseline characteristics associated with an increased risk of ICH; efficacy results suggest a reduced but still favorable clinical outcome</td>
</tr>
<tr>
<td>Gastrointestinal or genitourinary bleeding</td>
<td>Warning: gastrointestinal or genitourinary bleeding within the past 21 d</td>
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