Stroke Update IVtPA

Vivien Lee, MD, FAAN
Associate Professor-Clinical
Department of Neurology
The Ohio State University Wexner Medical Center

Time lost is brain lost!

Stroke 2006

• Each 59 seconds, an ischemic stroke will have killed 1.9 million brain cells, according to a study published in Stroke: Journal of the American Heart Association

Ischemic penumbra

Acute stroke treatment:
1) Intravenous tissue plasminogen activator (IVtPA)
2) Intra-arterial therapy (IAT), i.e. mechanical thrombectomy

Stroke thrombolysis

Save a Minute, Save a Day

Stroke 2014

• disability-adjusted life years (DALYs)
  In each minute saved provided a mean 1.8 days of DALY
• patients gain an equivalent of at least a day of healthy life for each minute saved
• Save a Minute, Save a Day
CASE A

- 71 y.o. RH female with a history of lung adenocarcinoma s/p LUL lobectomy
- POD 8 lobectomy who at 1am developed witnessed onset of left hemiparesis
- Stroke code was called at 5am
- She had a Chest tube
- Initial NIHSS was 11
- CT brain negative
- BP, labs (coags, BS, etc) WNL

**Question:** Recommend IVtPA?

Clinical course

- She received tPA at 529a (4 h 29 min)
- CTA/P

Clinical Course

- Cerebral angiogram negative
- MRI shows small right MCA infarct

- The next day neurological examination showed left hemiparesis, NIHSS-3
- She was transferred to ARF PSD #7
- Follow in stroke clinic at 3 months, mRS-1, NIHSS 0

Thrombolytics
Activase (tPA)

- produced by recombinant DNA technology
  - synthesized using the complementary DNA (cDNA) for natural human tissue-type plasminogen activator obtained from a human melanoma cell line
  - purified glycoprotein of 527 amino acids
- sterile, white, lyophilized powder for IV administration after reconstitution with sterile Water
- supplied in 50 mg and 100 mg vials without vacuum
- duration of action 2-10 min

Intracranial hemorrhage

Incidence of Intracranial Hemorrhage in AMI patients

<table>
<thead>
<tr>
<th>Dose</th>
<th>Pt #</th>
<th>ICH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100mg, 3 hr</td>
<td>3272</td>
<td>0.4</td>
</tr>
<tr>
<td>&lt; 100mg, accelerated</td>
<td>10,396</td>
<td>0.7</td>
</tr>
<tr>
<td>150mg</td>
<td>1779</td>
<td>1.3</td>
</tr>
<tr>
<td>1-1.4 mg/kg</td>
<td>234</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Dose used in stroke patients
- IV tPA 0.9 mg/kg total dose (maximum 90 mg)
  - 10% as bolus over 1 minute
  - remaining 90% as infusion over 60 minutes

- Randomized double-blinded, placebo-controlled study
- 624 pts w/in 3 hr of onset, required pre-tx CT
- 0.9 mg/kg IV tPA (max 90mg) 10% bolus over 1 m, then remainder over 60 m
  - BP < 185/110

Part I- 291 pts, improve 4 on NIHSS in 24 hr
Part II- 333 pts, clinical outcome at 3 mos
  - NIH, Barthel, Modified rankin

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THERAPEUTIC EVALUATION OF a-THROMBOPLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

The Therapeutic Evaluation of a-THROMBOPLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE Group"
**NINDs Inclusion Criteria**

- Ischemic stroke with a clearly defined time of onset
- Deficit measurable on the NIHSS
- Base-line CT brain that showed no intracranial hemorrhage

**NINDs Exclusion Criteria**

- Stroke or serious head trauma within the preceding 3 mos
- Undergone major surgery within 14 days
- History of intracranial hemorrhage
- SBP >185 mm Hg or DBP >110 mm Hg
- Rapidly improving or minor symptoms
- Symptoms suggestive of SAH
- GI hemorrhage or urinary tract hemorrhage within 21 days
- Arterial puncture at a noncompressible site within 7 days
- Seizure at the onset of stroke
- Patients taking anticoagulants or who had received heparin within the 48 hours preceding the onset of stroke and had an elevated aPTT
- Prothrombin times > 15 seconds, platelet <100,000 per cubic millimeter, or glucose <50 mg or >400 mg per deciliter
- Aggressive treatment required to reduce blood pressure

**NINDs**

- Part I - Change in NIHSS
  - No significant difference
- Part II - Outcome at 3 months
  - Modified rankin scale (0-6)
    - 0 no symptoms at all
    - 1 no significant disability despite symptoms, able to carry out all usual duties and activities
  - 30% more likely to have minimal disability at 3 mos in tPA group
  - Absolute increase in favorable outcome 11% - 13%
**NINDs**

- Hemorrhage  
  - 6.4% tPA vs 0.6% placebo
- Mortality rate at 3 mo  
  - 17% tPA vs 21% placebo
- Interpretation: tPA w/in 3 hr window improves 3 month outcome
- FDA approval 1996

**IVtPA trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Pt #</th>
<th>Max dose (mg)</th>
<th>Window (hrs)</th>
<th>Symptomatic ICH % (tPA vs placebo)</th>
<th>Mortality % (tPA vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDs</td>
<td>624</td>
<td>0.9 (0.9)</td>
<td>&lt;3</td>
<td>6.4 vs 0.6</td>
<td>17.4 vs 20.8</td>
</tr>
<tr>
<td>ECASS I</td>
<td>620</td>
<td>100 (1.1)</td>
<td>&lt;6</td>
<td>19.8 vs 6.5*</td>
<td>22 vs 15.6</td>
</tr>
<tr>
<td>ECASS II</td>
<td>760</td>
<td>50 (0.9)</td>
<td>&lt;6</td>
<td>8.8 vs 3.4</td>
<td>10.5 vs 10.7</td>
</tr>
<tr>
<td>ATLANTIS B</td>
<td>447</td>
<td>90 (0.9)</td>
<td>3-5</td>
<td>7.0 vs 1.1</td>
<td>11.0 vs 6.9</td>
</tr>
</tbody>
</table>

Initiated in 1991, protocol similar to NINDs in 1993, study changed to 0-5hr due to safety concerns in 5-6 hr group. In 1996 (FDA approved tPA in first 3 hr) modified to 3-5 hr window. Trial terminated 1998 interim analysis suggested that detection of a beneficial effect of tPA was highly unlikely.

Extended IVtPA window (3-4.5 h)  
Similar to NINDs protocol

**ECASS 3 2008**

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke  

Extended IVtPA window (3-4.5 h)  
Similar to NINDs protocol

**ECASS 3**

- Enrolled 821
- More patients had a favorable outcome with alteplase than with placebo (52.4% vs 45.2%; OR, 1.34; 95% CI, 1.02 to 1.76; P = 0.04)
- Symptomatic ICH, 2.4% vs 0.2%; P = 0.008
- Mortality did not differ significantly between the alteplase and placebo groups
What is considered stroke onset?

- Witnessed onset
- If un-witnessed onset, then considered to be last known normal
- If fell asleep at midnight, awoke at 6 am with neurologic deficits
  - Arrived at ER by 7 am
  - Onset of symptoms is considered to be 7 hours ago, not 1 hour

Time of onset = Last known normal

Patient friendly visual

32 patients are better
3 are worse
(1 much worse)
65 are same

Source: UCLA Stroke Center (CC BY 4.0)

The evolution of the AHA GUIDELINES

AHA Guidelines 2007
Extended IVtPA window to 4.5hrs

- rtPA should be administered to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke (Class I Recommendation, Level of Evidence B)

AHA Guidelines 2013

- DTN time should be within 60 minutes from hospital arrival (Class I; Level of Evidence A)
- NOAC - not recommended unless the patient has not received a dose of these agents for >2 days (assuming normal renal metabolizing function). (Class III; Level of Evidence C)

AHA 2015 Guidelines Update IAT

1. Patients eligible for IVtPA should receive IV-tPA even if IAT is being considered (Class I; Level of Evidence A).
2. Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria (Class I; Level of Evidence A).
   a) prestroke mRS score 0 to 1
   b) acute ischemic stroke receiving IV-tPA within 4.5 hours of onset
   c) occlusion of the internal carotid artery or proximal MCA (M1)
   d) age ≥ 18 years
   e) NIHSS score of ≥ 6
   f) ASPECTS of ≥ 6, and
   g) treatment can be initiated (groin puncture) within 6 hours of onset

AHA 2015 Guidelines Update IAT

3. As with IV-tPA, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI grade 2b/3 should be achieved as early as possible and within 6 hours of stroke onset (Class I; Level of Evidence B-R)
AHA 2015 Scientific Statement- IV-tPA

AHA 2015 Update, consider

- Rapidly improving but still potentially disabled
- Pregnancy
- Major surgery within 14 days (excludes intracranial intraspinal)
- Seizure at onset
- Dural puncture within 7 days
- Psychogenic, malingering, conversion
- Acute MI or Recent MI
- GI bleeding (warning, structural lesion or within 21 days)
- Unruptured cerebral aneurysm (not giant)
- EICs on CT (mod)
- Cervical artery dissection
- Menstruation

AHA 2015, DO NOT recommend

- Hemorrhage on CT
- Prior ICH
- Bleeding diathesis
  - Coumadin INR > 1.7
  - NOAC (within 48 hrs)
  - Lovenox (prophylactic and treatment dose) – FIXED IN 2018
- BS < 50 or > 400
- Aortic Arch Dissection
- Endocarditis
- Intra-axial neoplasm (excludes meningioma)

AHA 2018 Guidelines

New recommendations

- CMBs
- Sickle cell
- Corrected LMWH “treatment dose within 24 hours”
- IAT- expanded to 24 hours window
Medical malpractice

Systematic Review of Malpractice Litigation in the Diagnosis and Treatment of Acute Stroke

Jack J. Hendriks, PhD, Lisa Cernak, BA candidate, Xuanjun Zhang, MS, Lindsay A. Lobb, BA, Jordan Rockwood, MD, J. M. Tocco, MD, MS, Christopher F. Selven, MD

Stroke 2019

- 3 legal databases were used to search
- 246 medical malpractice cases related to acute management of ischemic stroke
  - 71 cases specifically alleged failure to treat with tPA
  - 1 case related to complications (hemorrhage) after tPA administration, dismissed via summary judgment
- Litigation related to a failure to give tPA is more common than for cases where tPA was administered

IV tPA limitations

Katzan. Arch Neur 2004

- t-PA has had limited impact on overall morbidity and mortality on a national level
  - restricted application to < 5% of patients with acute stroke
  - strict time window
  - delay in presentation the most common reason patients were ineligible for IV thrombolysis
- Only 15% of patients arrived within the 3-hour time window for intravenous IV tPA
- Subset of large vessel occlusions LVO (NIHSS>20) poor recanalization rates

Incidence and Predictors of Early Recanalization After Intravenous Thrombolysis

A Systematic Review and Meta-Analysis

Fious Souza, MD; Guillaume Tinc, PhD; Bernard Main, MD, Jean-Louis Mos, MD; Catherine Oppenheim, PhD; Jean-Charles Barro, PhD

Stroke 2016

- Early recanalization (ER; ≤ 3 hours after start of IV-tPA)
- Meta-analyses, 26 studies, 2063 patients
- Overall incidence of partial or complete ER was 33% (95% CI, 27–40), varied according to occlusion site:
  - 35% (complete ER 21%) for proximal MCA
  - 13% (complete ER 4%) for ICA
  - 13% (complete ER 4%) for basilar occlusion
- Proximal occlusion and higher NIHSS were the most consistent no-ER predictors

Thrombectomy for Large Vessel Occlusion (LVO)

Ciarán J. Powers, MD, PhD, FAANS
Associate Professor
Department of Neurological Surgery
Surgical Director, Comprehensive Stroke Center
The Ohio State University Wexner Medical Center
### Financial Disclosures

- Clinical Research Support: Medtronic, MicroVention and Stryker Neurovascular
- Fellowship Support: Medtronic

### Overview

- Thrombectomy for Large Vessel Occlusion (LVO)
  - MR CLEAN and friends
- Thrombectomy beyond 6 hours
  - DAWN and DEFUSE 3

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**THROMBECTOMY FOR LVO**
TICI

- Grade 0 = No perfusion.
- Grade 1 = Perfusion past the initial obstruction, but limited distal branch filling with little or slow distal perfusion.
- Grade 2a = Perfusion of less than ½ of the vascular distribution of the occluded artery (e.g., filling and perfusion through 1 M2 division).
- Grade 2b = Perfusion of ½ or greater of the vascular distribution of the occluded artery (e.g., filling and perfusion through 2 or more M2 divisions).
- Grade 3 = Full perfusion will filling of all distal branches.

STUDIES SUPPORTING THROMBECTOMY

- Patient population
  - Greater than 18 years with no upper age limit
  - NIHSS greater than or equal to 2
- Imaging
  - Exclude hemorrhagic stroke by CT
  - Occlusion by CTA, MRA or DSA
- Intervention
  - Intra-arterial thrombectomy within 6 hours with or without IV rtPA in patients with intracranial occlusion in anterior circulation artery (ICA, M1, M2, A1 or A2)
### Study Stats
- **Size:** 500 study participants
  - Mean age: 65 years (23 to 96 years)
  - Men: 58.4%
  - 95% of patients in both groups had pre-stroke mRS 2 or better
  - Mean NIHSS: 17
- **267 patients (53.4%)** assigned to control
- **233 patients (46.6%)** assigned to intervention
- 196 underwent IA therapy
  - 195 patients underwent mechanical thrombectomy
    - 190 with stent-retriever
  - 88 patients (37.8%) had general anesthesia
  - 30 patients (12.9%) underwent concurrent carotid stent
  - 24 patients (10.3%) received additional IA thrombolytic
  - 1 patient (0.4%) underwent IA tPA only

### Results
- **Primary**
  - Median mRS at 90 days: 3 in Intervention and 4 in Control.
- **Secondary**
  - mRS 0-3 at 90 days: 51% in Intervention and 35% in Control.
  - Persistent vessel patency: 75% in Intervention and 33% in Control.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>mRS 0-1 90 days</td>
<td>27 (12%)</td>
</tr>
<tr>
<td>mRS 0-2 90 days</td>
<td>76 (35%)</td>
</tr>
<tr>
<td>mRS 0-3 90 days</td>
<td>109 (51%)</td>
</tr>
<tr>
<td>NIHSS 24 h median</td>
<td>12 (2-20)</td>
</tr>
<tr>
<td>Persistent vessel patency</td>
<td>141/187 (75.4%)</td>
</tr>
<tr>
<td>Infarct volume median</td>
<td>49ml (22-96)</td>
</tr>
</tbody>
</table>

### OPTIONS
- **Endovascular Therapy for Ischemic Stroke with Perfusion-imaging Selection**
- **Original Article**: Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial
  - **Primary outcome**
    - Reperfusion at 24 hours defined by percent reduction in perfusion-lesion volume between initial and 24-hour CT perfusion studies
  - **Secondary outcome**
    - mRs at 90 days
    - Symptomatic hemorrhage
    - SAH
    - Parenchymal hematoma within 36 hours after treatment with increase in NIHSS by 4 or more points
    - Death due to any cause

- **EXTEND IA**: After MR CLEAN published, study arrested

- **Original Article**: Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial

- **Secondary outcome**
  - mRs at 90 days
  - Symptomatic hemorrhage
  - SAH
  - Parenchymal hematoma within 36 hours after treatment with increase in NIHSS by 4 or more points
  - Death due to any cause
Patient population
- Greater than 18 years with no upper age limit
- Functional independence before stroke onset

Imaging
- CT
  - Exclude hemorrhagic stroke
  - ASPECTS (Alberta Stroke Program Early Computerized Tomography Score), used in ASPECTS to identify patients with small infarct core defined by ASPECT score 6-10
  - CTA evaluated for occlusion AND also assess for moderate-to-good vascular collateralization in setting of LVO, which was defined at filling of at least 50% of the MCA pial artery circulation

Intervention
- Intra-arterial thrombectomy within 6 hours with or without IV tPA in patients with intracranial occlusion in anterior circulation artery (ICA, M1, M2)

Primary outcome
- Modified Rankin scale (mRS) at 90 days

Secondary outcome
- Early recanalization and reperfusion
- Intracranial hemorrhage
- Angiographic complications
- Neurological disability at 90 days
- Death

Imaging outcomes

Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke

Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times

MR CLEAN
EXTEND IA
ESCAPE

Trends over time in complete reperfusion rates in active arms of coronary (diamond) and cerebral (square) reperfusion trials, without sample size weighting and with spontaneous reperfusion rates placed in 1980 as anchor, pre-reperfusion therapy era, values.


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THROMBECTOMY BEYOND 6 HOURS
Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging

- **Patient population**
  - Occlusion of intracranial ICA or M1
  - Initial infarct size of less than 70 ml AND ratio of the volume of ischemic tissue on perfusion imaging to infarct volume of 1.8 or more
- **Intervention**
  - Intra-arterial thrombectomy between 6-16 hrs from LKW
- **Primary outcome**
  - Modified Rankin scale (mRS) at 90 days
- **Secondary outcome**
  - Functional independence (mRS 0-2) at 90 days
  - Infarct volume, lesion growth, reperfusion and recanalization at 24 hours
  - Modified TICI score of 2b or 3 for thrombectomy patients

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**Neuroimaging Inclusion Criteria**

MRA / CTA reveals
- M1 segment MCA occlusion, or
- ICA occlusion (cervical or intracranial); with or without tandem MCA lesions

AND

TargetMismatch Profile on CT perfusion or MRI (RAPID)
- Ischemic core volume < 70 mL
- Mismatch ratio > 1.8
- Mismatch volume ≥ 15 mL
**RAPID Imaging**

- CBF (<30%) volume: 26.4 ml
- Perfusion (Max<1.8a) volume: 129.4 ml
- Mismatch volume: 103.0 ml
- Mismatch ratio: 69

**Study Stats**

- Size: 182 study participants
  - Mean age: 70 years
  - Men: 54%
  - Median NIHSS: 16
- 90 patients assigned to control
- 92 patients assigned to thrombectomy

**Results**

**Patient population**
- Occlusion of intracranial ICA or M1
- Group A: ≥80 yrs, NIHSS ≥10, infarct ≤20 ml
- Group B: <80 yrs, NIHSS ≥10, infarct ≤30 ml
- Group C: <80 yrs, NIHSS ≥20, infarct 30-50 ml

**Imaging**
- Exclude hemorrhagic stroke by CT
- Occlusion by CTA, MRA or DSA
- Infarct volume by MRI or CT perfusion

**Intervention**
- Intra-arterial thrombectomy with Trevo device between 6-24 hrs from LKW

**Primary outcome**
- Utility-weighted modified Rankin scale (mRS) at 90 days
- Functional independence (mRS 0-2) at 90 days

**Secondary outcome**
- Early therapeutic response (decrease of NIHSS ≥10 or NIHSS of 0-1)
- Death at 90 days
- TICI 2b-3

**DAWN**

Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

- Occlusion of intracranial ICA or M1
- Group A: ≥80 yrs, NIHSS ≥10, infarct ≤20 ml
- Group B: <80 yrs, NIHSS ≥10, infarct ≤30 ml
- Group C: <80 yrs, NIHSS ≥20, infarct 30-50 ml

- Exclude hemorrhagic stroke by CT
- Occlusion by CTA, MRA or DSA
- Infarct volume by MRI or CT perfusion

- Intra-arterial thrombectomy with Trevo device between 6-24 hrs from LKW

- Utility-weighted modified Rankin scale (mRS) at 90 days
- Functional independence (mRS 0-2) at 90 days

- Early therapeutic response (decrease of NIHSS ≥10 or NIHSS of 0-1)
- Death at 90 days
- TICI 2b-3
Study Stats

- Size: 206 study participants
  - Mean age: 70 years
  - Age ≥80 yrs: 25%
  - Men: 45%
  - Median NIHSS: 17
- 99 patients assigned to control
- 107 patients assigned to intervention with Trevo device

Summary

- Thrombectomy for Large Vessel Occlusion (LVO)
  - Patients with LVO benefit from thrombectomy up to 24 hours from last known well
  - The window for thrombectomy can be determined by functional imaging