Updates in Management of Acute Ischemic Stroke

A presentation for HealthTrust Members
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Disclosures

• The presenter has no financial relationships with any commercial interests pertinent to this presentation.

• This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand or drug.
Objectives

Pharmacist

• Identify the pharmacist’s role in the management of patients with acute ischemic stroke (AIS)
• Discuss the updated recommendations for the use of systemic fibrinolytic therapy for AIS
• Review the updated recommendations for adjunctive and/or alternative pharmacologic and nonpharmacologic therapies for AIS

Technician

• Recall the difference between hemorrhagic and ischemic strokes
• Identify brand and generic drugs names for medications used to treat strokes
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIS: acute ischemic stroke</td>
<td>DWI: diffuse weighted imaging</td>
</tr>
<tr>
<td>ASPECTS: Alberta Stroke Program Early CT score</td>
<td>ED: emergency department</td>
</tr>
<tr>
<td>AVM: atrioventricular malformation</td>
<td>EMS: emergency medical services</td>
</tr>
<tr>
<td>BA: basilar artery</td>
<td>HTN: hypertension</td>
</tr>
<tr>
<td>BP: blood pressure</td>
<td>ICA: internal carotid artery</td>
</tr>
<tr>
<td>CPSS: Cincinnati Prehospital Stroke Score</td>
<td>LAPSS: LA Prehospital Stroke Screen</td>
</tr>
<tr>
<td>CT scan: computerized tomography scan</td>
<td>LMWH: low molecular weight heparin</td>
</tr>
<tr>
<td>CTA: CT angiogram</td>
<td>M1: middle cerebral artery segment 1</td>
</tr>
<tr>
<td>DAPT: dual antiplatelet therapy</td>
<td>M2: middle cerebral artery segment 2</td>
</tr>
<tr>
<td>DOAC: direct oral anticoagulant</td>
<td>MCA: middle cerebral artery</td>
</tr>
<tr>
<td>DTN time: door to needle time</td>
<td>MI: myocardial infarction</td>
</tr>
</tbody>
</table>
Key Symbols

Stroke guideline updates and new recommendations

Highlighting the pharmacist’s role
Stroke Epidemiology in the US

**Incidence**
- 1 stroke every 40 seconds
- 87% ischemic, 13% hemorrhagic

**Mortality**
- 1 death every 3.75 mins
- 5th leading cause of death

**Morbidity**
- Leading cause of serious long-term disability

“Code Stroke” Overview
Education

BE-FAST

B Balance: dizzy, trouble walking/ balancing
E Eyes: vision changes
F Facial droop, numbness
A Arm weakness or drift
S Speech: slurred speech, unable to talk
T Time to call 911!!

“Code Stroke” Overview
Prehospital Care

Cincinnati Prehospital Stroke Score (CPSS)
- Facial Droop
- Arm Drift
- Speech

LA Prehospital Stroke Screen (LAPSS)
- Age >45
- History of seizure
- New onset (within 24 hrs.)
- Neurologic symptoms
- Ambulatory at baseline
- Blood glucose
- Asymmetry: facial droop, arm drift, grip

Sources:
“Code Stroke” Overview
Initial Evaluation

• Assessment of ABC’s
• Vital signs, physical exam
  • Blood glucose
• Neurological exam, NIHSS
• Symptom onset, “last known normal”
• History: co-morbidities, medications
• Diagnostic imaging

“Code Stroke” Overview
“Code Stroke” Overview
Fibrinolytic Therapy

tPA (Activase®): 0.9 mg/kg, max 90 mg

Figure 1: Fibrinolysis. Accessed from https://basicmedicalkey.com/drug-therapy-of-thromboembolic-disorders/
Alteplase: Inclusion Criteria

- Symptom onset within 3 hours
- Symptom onset within 3-4.5 hours, with additional criteria
- AIS with measurable neurologic deficit
- Age $\geq 18$ years

Alteplase: Inclusion Criteria

- Symptom onset within 3 hours
- Symptom onset within 3-4.5 hours, with additional criteria
- AIS with measurable neurologic deficit
- Age ≥18 years
  - Mild but disabling stroke symptoms
  - Sickle cell patients are eligible for tPA

*tPA may be reasonable in patients with:*
- Mild stroke between 3-4.5 hours
- 1-10 previous cerebral microbleeds
- >10 previous cerebral microbleeds, if potential for substantial benefit

### Alteplase: Exclusion Criteria

#### Absolute

- Modifiable: BP >185/110; blood glucose <50mg/dL
- Intracranial hemorrhage (current, or history of)
- Active internal bleeding
- AIS or severe head trauma within 3 mo
- Warfarin with INR >1.7 or PT>15 secs
- DOAC use within 48 hours
- Acute bleeding diathesis
- Recent intracranial or intraspinal surgery
- Intracranial neoplasm, AVM, or aneurysm
- CT with multilobar infarction

#### Relative

- Minor symptoms
- Rapidly improving symptoms
- Pregnancy
- Seizure + postictal neurologic impairments
- Recent major surgery/trauma, hemorrhage, or MI
- Within 3-4.5 hours: Age >80 years, severe stroke (NIHSS >25), any oral anticoagulant, history of both diabetes + prior AIS

---

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- Recent major surgery/trauma, hemorrhage, or MI
- Within 3-4.5 hours: Age >80 years, severe stroke (NIHSS >25), any oral anticoagulant, history of both diabetes + prior AIS, and imaging evidence of ischemia in >1/3rd MCA territory

#### Treatment dose of LMWH

Goal DTN Time

DTN time: within 60 minutes of from hospital arrival

Primary goal: DTN time within 60 minutes in >50%
Secondary goal: Reasonable to aim for DTN times within 45 minutes in >50%

Goal DTN Time

DTN time: within 60 minutes of from hospital arrival

Primary goal: DTN time within 60 minutes in >50%
Secondary goal: Reasonable to aim for DTN times within 45 minutes in >50%

## Improving DTN Time

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Median DTN</td>
<td>48 min vs 73 min</td>
<td>46 min vs 58 min</td>
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| DTN Goal Achieved          | ≤60min: 71% vs 29%  
≤45min: 44% vs 9% | ≤60min: 71% vs 61%  
≤45min: 49% vs 25%           |
| Other factors that may affect DTN | More pts over weekend/overnight in no PharmD group  
(statistical analysis: did not significantly affect DTN)  
No difference in HTN  
No difference in time to imaging | Arrival by EMS and tPA reconstitution in ED associated with lower DTN  
No difference in HTN |
| Safety                     | N/A                                                                           | No PharmD: 2 errors  
(reconstitution, infusion rate) |
## Improving DTN Time

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<tr>
<td><strong>Study</strong></td>
<td>Retrospective, n=125 PharmD vs. no PharmD</td>
<td>Retrospective, n=100 PharmD vs. no PharmD</td>
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| **DTN Goal Achieved** | <60 minutes: 71% vs. 29%  
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(statistical analysis: did not significantly affect DTN)  
No difference in HTN  
No difference in time to imaging  | Arrival by EMS and tPA reconstitution in ED associated with lower DTN  
No difference in HTN |
| **Safety**     | N/A                                                                           | No PharmD: 2 errors  
(reconstitution, infusion rate) |

Pharmacist independently associated with improved DTN

### Alternative Fibrinolytic Therapy

TNK (TNKase®): optimal dose and indication not determined

<table>
<thead>
<tr>
<th>Designation</th>
<th>Amino Acid Substitution</th>
<th>Effect Compared to tPA</th>
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<tbody>
<tr>
<td>T</td>
<td>Thr-103 → Asn</td>
<td>↓ decreased clearance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ fibrin binding</td>
</tr>
<tr>
<td>N</td>
<td>Asn-117 → Gln</td>
<td>↓ decreased clearance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Restores fibrin binding</td>
</tr>
<tr>
<td>K</td>
<td>Lys-His-Arg-Arg (296-299) → Ala-Ala-Ala-Ala</td>
<td>↑ fibrin specificity by 15 fold</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ resistance to PAI-1</td>
</tr>
<tr>
<td></td>
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<td>↓ degradation by 80 fold</td>
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## Tenecteplase for AIS

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<th>NOR-TEST</th>
<th>EXTEND-IA TNK</th>
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<td>Study</td>
<td>Prospective, randomized, blinded endpoint, superiority</td>
<td>Prospective, randomized, blinded endpoint</td>
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<tr>
<td>Patients</td>
<td>N=1100 AIS eligible for thrombolytic +/- MT Median: NIHSS 4 (2-8), age 77 NIHSS 0-7: 78% vs 73%</td>
<td>N=204 ICA, M1, M2, or BA AIS eligible for thrombolytic + MT within 6 hours Median: NIHSS 17 (12-22), age 71 M1 stroke: ~60%</td>
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<td>Intervention</td>
<td>Bolus TNK 0.4 mg/kg (max 40mg) tPA 0.9 mg/kg (max 90mg)</td>
<td>Bolus TNK 0.25 mg/kg (max 25mg) tPA 0.9 mg/kg (max 90mg)</td>
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<td>Results</td>
<td>mRS 0-1 at 3mo: 64% vs 63% mRS 0-2 at 3mo: 77% vs 78% sICH at 24hrs: 3% vs 2% Mortality at 3mo: 5% vs 5%</td>
<td>Substantial reperfusion: 22% vs 10% mRS 0-1 at 3mo: 51% vs 43% mRS 0-2 at 3mo: 64% vs 51% sICH: at 24 hrs: 1% vs 1% Mortality: 10% vs 18%</td>
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<td>Conclusion</td>
<td>TNK similar functional outcomes and safety outcomes as tPA in mild stroke</td>
<td>TNK +MT higher incidence of reperfusion and functional outcome than tPA +MT in proximal artery stroke</td>
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<td>outcomes as tPA in mild stroke</td>
<td>than tPA +MT in proximal artery stroke</td>
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</table>

Tenecteplase 0.4mg/kg not proven superior or noninferior to tPA

May be considered as alternative in patients with mild neurologic impairment and no major intracranial occlusion (IIb-BR)

## Future of Tenecteplase for AIS

### Upcoming Phase 3 Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Intervention</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATTEST-2</td>
<td>AIS within 4.5 hrs, no planned MT</td>
<td>TNK 0.25 mg/kg</td>
<td>tPA 0.9 mg/kg</td>
</tr>
<tr>
<td>EXTEND-IA TNK 2</td>
<td>Major occlusion AIS within 4.5 hrs</td>
<td>TNK 0.4 mg/kg + MT</td>
<td>TNK 0.25 mg/kg + MT</td>
</tr>
<tr>
<td>NOR-TEST 2</td>
<td>AIS within 4.5</td>
<td>TNK 0.4 mg/kg +/- MT</td>
<td>tPA 0.9 mg/kg +/- MT</td>
</tr>
<tr>
<td>TASTE</td>
<td>AIS within 4.5 hrs, no planned MT</td>
<td>TNK 0.25 mg/kg</td>
<td>tPA 0.9 mg/kg</td>
</tr>
<tr>
<td>TIMELESS</td>
<td>ICA or MCA AIS within 4-24 hrs</td>
<td>TNK 0.25 mg/kg</td>
<td>Placebo</td>
</tr>
<tr>
<td>TEMPO-2</td>
<td>AIS within 12 hrs with minor stroke</td>
<td>TNK 0.25 mg/kg</td>
<td>Antiplatelet</td>
</tr>
<tr>
<td>TWIST</td>
<td>Wake up stroke</td>
<td>TNK 0.25 mg/kg</td>
<td>Standard of care</td>
</tr>
</tbody>
</table>

**Bottom line:** Expect greater discussion about TNK, but tPA will remain the primary thrombolytic for AIS

Sources: Clinicaltrials.gov/
Anzctr.org.au/
Assessment 1: Pharmacists

Which of the following is not an absolute contraindication to thrombolytic therapy?

A. Severe head trauma within 3 months
B. Extra-axial intracranial neoplasms
C. Treatment dose of low molecular weight heparins
D. Last-known-normal 8 hours prior to presentation
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A. Severe head trauma within 3 months
B. Extra-axial intracranial neoplasms
C. Treatment dose of low molecular weight heparins
D. Last-known-normal 8 hours prior to presentation
Assessment 2: Technicians

Which of the following medications are thrombolytics?

A. Clopidogrel (Plavix ®)
B. Tenecteplase (TNKase ®)
C. Alteplase (Activase ®)
D. Aspirin
E. B and C
Response 2: Technicians

Which of the following medications are thrombolytics?

A. Clopidogrel (Plavix ®)
B. Tenecteplase (TNKase ®)
C. Alteplase (Activase ®)
D. Aspirin
E. B and C
“Code Stroke” Overview
# Mechanical Thrombectomy

Fibrinolytic therapy received if eligible

Evaluate eligibility for MT

Do NOT delay to assess for improvement following fibrinolytic therapy

## 2018 Recommendation Criteria for Endovascular Management

<table>
<thead>
<tr>
<th>2018 Recommendation</th>
<th>Criteria for Endovascular Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>• Pre-stroke mRS 0 to 1</td>
</tr>
<tr>
<td></td>
<td>• M1, ICA</td>
</tr>
<tr>
<td></td>
<td>• Age ≥ 18</td>
</tr>
<tr>
<td></td>
<td>• NIHSS &gt; 6</td>
</tr>
<tr>
<td></td>
<td>• ASPECTS ≥ 6</td>
</tr>
<tr>
<td></td>
<td>• Symptom onset within 6 hours</td>
</tr>
<tr>
<td>IA</td>
<td>• LKW 6 – 16 hours (DEFUSE3 criteria)</td>
</tr>
<tr>
<td>IA</td>
<td>• LKW 6 – 24 hours (DAWN criteria)</td>
</tr>
<tr>
<td>IIa,B-R</td>
<td>• LKW 6 - 24 hours (DAWN criteria)</td>
</tr>
<tr>
<td>IIb, B-R</td>
<td>• Consider if M2 or M3, within 6 hours of symptom onset</td>
</tr>
<tr>
<td>IIb, B-R</td>
<td>• Consider if pre-stroke mRS &gt;1, ASPECTS &lt;6, or NIHSS &lt;6 with ICA or M1 stroke within 6 hr onset window</td>
</tr>
<tr>
<td>IIb, C-EO</td>
<td>• Consider if anterior cerebral, vertebral, basilar, or posterior cerebral arteries</td>
</tr>
</tbody>
</table>

Determining MT Eligibility

Identification of ischemic vessel (MCA, ICA) & carotid stenosis

CTA or MRA

ASPECTS

CT or DWI (MRI)

Expanding the MT Window

DEFUSE-3 (6-16 hours)

- ≤ 90 yo
- NIHSS ≥ 6
- Infarct core <70 mL
- Ischemic tissue vol to initial infarct ratio ≥ 1.8
- Penumbra ≥ 15 mL

DAWN (6-24 hours)

- 80 yo + NIHSS ≥ 10 + infarct < 21 mL
- < 80 yo+ NIHSS ≥ 10 + infarct < 31 mL
- < 80 + NIHSS ≥ 20 + infarct of 31 to < 51 mL

Pharmacist Role in MT

• If eligible for thrombolytic therapy, do not delay administration of IV thrombolytic for additional imaging and/or MT
  • Facilitate logistics of IV thrombolytic
  • tPA vs. TNK – more to come?

• Blood pressure management: limited data
  • In patients undergoing MT, maintain BP ≤180/105 during and for 24 hours following procedure
  • In patients undergoing MT with successful reperfusion, maintain BP <180/105

“Code Stroke” Overview
## Antiplatelets

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Aspirin                     | Recommended within 24-48 hours  
Delay aspirin for 24 hours following IV tPA. May consider earlier initiation based on comorbidities |
| IV eptifibatide and IV tirofiban | Phase II trials have suggested safety; efficacy not well established. Further clinical trials are needed |
| IV abciximab                | Potentially harmful; not recommended. May be associated with significant increased risk of ICH without improvement in mortality or disability |
| Aspirin + clopidogrel       | In minor stroke, initiating DAPT within 24 hours for 21 days may reduce early secondary strokes for up to 90 days |
| Tigacrelor                  | Not recommended over aspirin in acute treatment of minor stroke. May be reasonable alternative if aspirin contraindicated |

Anticoagulants

“Not well established”

“Further clinical trials needed”

Ongoing studies for factor Xa inhibitors – more to come?

## Acute Blood Pressure Management

<table>
<thead>
<tr>
<th>AIS Management</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>tPA</td>
<td>&lt;180/105 for first 24 hours following tPA</td>
</tr>
<tr>
<td>MT</td>
<td>&lt;180/105 for first 24 hours might be reasonable</td>
</tr>
</tbody>
</table>
| Maximal medical therapy (no tPA or MT) | If BP <220/120: no benefit to HTN treatment within 48-72 hours  
If BP >220/120: benefit of HTN treatment within 48-72 hours uncertain. Might be reasonable to lower BP by 15% during first 24 hours |
| Emergent co-morbidity* | Lowering BP initially by 15% is probably safe |

*concomitant acute coronary event, acute heart failure, aortic dissection, post thrombolysis sICH, or preeclampsia/eclampsia

Pharmacist Role Recap

- Education: community, prehospital & hospital services
- Patient evaluation & history
- Facilitating thrombolytic therapy to reduce DTN
  - Management of adverse effects
- Blood pressure management
- Antiplatelet therapy
Assessment 3: Pharmacists

What is the recommended blood pressure goal in the first 24 hours following mechanical thrombectomy?

A. <220/120  
B. <180/105  
C. <185/110  
D. <160/100
Assessment 3: Pharmacists

What is the recommended blood pressure goal in the first 24 hours following mechanical thrombectomy?

A. <220/120
B. <180/105
C. <185/110
D. <160/100
Assessment 4: Technicians

Thrombolytics are used for what type of stroke?

A. Ischemic
B. Hemorrhagic
Response 4: Technicians

Thrombolytics are used for what type of stroke?

A. Ischemic
B. Hemorrhagic
Thank you!

Raghad Saadi, PharmD
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