Updates in Stroke

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April 2, 2022
More than 795,000 people in U.S. have stroke annually (5th leading cause of death)

1 stroke every 40 seconds

1 death from stroke every 4 minutes

Approximately 87% of strokes are ischemic type

Stroke related costs = $46 billion/ year (health care services, medicines for stroke treatment, missed days of work)
Risk of first stroke is almost twice as high for black people as for white. Black people have the highest mortality rate due to stroke.

Overall death rates from stroke have declined for decades in all race/ethnicities except Hispanic people for whom rates have increased since 2013.

34% of people hospitalized for stroke were under age 65 in 2009.

Major risk factors include high blood pressure, high cholesterol, smoking, obesity, and diabetes. 1 in 3 U.S. adults has at least one of these.

https://www.cdc.gov/stroke/facts.htm
Turning Points in Stroke Care

- Alteplase found to be effective for acute stroke therapy within 3 hours (1996)
- Alteplase shown to be effective up to 4.5 hours (2008)
- Mechanical thrombectomy shown to be effective for treatment of large vessel occlusions within 6 hours (2015)
- Mechanical thrombectomy treatment window extended to 24 hours (2018)
Earlier stroke treatment leads to less disability

Time is Brain

Only 15-32% of stroke patients present to ED within 3 hours. 40-50% will be eligible for tPA

Less than 5% of ischemic stroke patients are treated with thrombolytic therapy

For good functional outcome, NNT = 4.5 at <1.5 hr,

NNT = 9 at 1.5-3 hr, NNT= 14.1 at 3-4.5 hr
Inside the MSU

**On the Unit**

- Standard ambulance equipment/medications
- CT scanner
- Point of care lab equipment
- Telemedicine capability
- tPA

**Team:** Physician, EMT, CT technologist, Nurse
MSU Efficacy (Early studies)

- Univ. of Saarland (1st RCT) showed 41 min decrease in time from stroke alert to treatment decision. No improvement in functional outcome at 7 days.
- Phantom-S pilot study showed decreased time to treatment. No adverse outcomes in those treated with tPA compared with treatment in the ED.
- Phantom-S RCT: 25 min decrease in treatment time, increased utilization of tPA, no changes in 7-day mortality or rate of hemorrhage.
  - Sub-study analysis showed increased rates of good functional outcome at 0-3 months and decreased 3-month mortality in MSU group.

MSU Efficacy (BEST-MSU)

Prospective, Multicenter, Controlled Trial of Mobile Stroke Units

MSU Efficacy (BEST-MSU)

- Observational, prospective, alternating week trial enrolling at 7 sites (>70% from Houston site)
- Enrolled 1515 patients (1047 received tPA)
- Median stroke onset to tPA time 72 min in MSU group vs 108 minutes in EMS group
- Of tPA eligible patients, 97.1% in MSU group were treated vs 79.5% in EMS group
- 2.6% of patients in EMS group vs 32.9% in MSU group treated in “golden hour”

MSU Cost Effectiveness

- No difference in length of stay or proportion discharged home
- MSU patients had more days at home without nursing home or rehospitalization at 1 year
- MSU patients reported better subjective average quality of life
- MSU patients had higher healthcare utilization costs ($57,658 vs $54,898)
- MSU annual operation cost estimate: $436,457
- Using $190,000/QALY threshold, NNT = 100-150 tPA eligible patients/year

MSU Implementation

- 20 MSU sites across the U.S. (2021)
- Houston and El Paso
- Improve Cost Effectiveness:
  - Reduce personnel using telemedicine
  - Determine number of units and placement to service a region efficiently
  - Expand scope to TBI, status epilepticus, intracranial hemorrhage
  - Improve accuracy of stroke identification algorithm from dispatch office

Thrombolytic Therapy: Alteplase

- Thrombolytic agent FDA approved for acute ischemic stroke, pulmonary embolism, acute MI, and occluded catheters.
- Mechanism: converts plasminogen to plasmin which lysed fibrin and fibrinogen
- Initial half life = 5 min
- Dose: 0.9 mg/kg given (10% given as IV bolus over 1 minute and 90% given as infusion over 1 hour)
- Adverse reactions: Bleeding, Angioedema, Anaphylaxis, Fever
Thrombolytic Therapy: Alteplase

- **NINDS (1995):** 0-3 hr window with disabling symptoms
- **ECASS (2008):** 3-4.5 hr window
- **WAKE-UP (2018):** Unknown last known well with MRI DWI/FLAIR mismatch
- **EXTEND (2019):** 4.5 – 9 hr window using CT or MRI perfusion mismatch
Thrombolytic Therapy: Tenecteplase

- A thrombolytic and tissue plasminogen activator
- Increased fibrin specificity which decreases systemic plasminogen activation and degradation of circulating fibrin
- Initial half life: 20-24 minutes
- Adverse reactions: Bleeding, Arrhythmia

(in use for coronary thrombolysis), Angioedema, Anaphylaxis

Thrombolytic Therapy: Tenecteplase

TNK S2B: No difference in 90-day neurologic outcomes between standard dose alteplase and 0.1 mg/kg or 0.25 mg/kg tenecteplase in 0-3 hr window

ATTEST: Tenecteplase 0.25mg/kg outcomes in 0-4.5 hr window equivalent to standard dose alteplase with trends toward better neuro outcome in tenecteplase group

EXTEND IA-TNK: Better reperfusion and neurologic functional outcomes in Tenecteplase 0.4mg/kg in 0-4.5 hr window prior to thrombectomy

TAAIS: Tenecteplase 0.25 mg/kg outcomes superior to standard dose alteplase in 0-6 hr window (25 patients enrolled)

NOR-TEST: Tenecteplase 0.4mg/kg outcomes equivalent to standard dose alteplase in 4.5 hr from onset or from wake-up window
# Thrombolytic Therapy: Tenecteplase

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Measurements</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of symptomatic hemorrhage</td>
<td>Baseline and after-treatment variables with symptomatic and asymptomatic</td>
<td>Following treatment with tenecteplase, there was a greater early clinical improvement with a median of 9 in comparison to alteplase’s median of 1 [13].</td>
</tr>
<tr>
<td></td>
<td>National Institutes of Health Stroke Scale score (NIHSS)</td>
<td>No significant difference between both scores because a majority of the score range fell between 0 and 4 for both interventions [16].</td>
</tr>
<tr>
<td>Functional outcome at 90 days</td>
<td>Modified Rankin Scale (mRS)</td>
<td>Both interventions shared the same effect [12, 16].</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A higher proportion of patients showed a significant recovery using the tenecteplase intervention [15].</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The proportion of patients with good functional outcome was 61% in the tenecteplase group and 57% in the alteplase group (odds ratio, 1.24; 95% CI 0.65–2.37).</td>
</tr>
<tr>
<td>Reperfusion rate after thrombectomy</td>
<td>Modified thrombolysis in cerebral infarction (mTICI)</td>
<td>Over the course of 90 days following the treatment, overall reperfusion rates were significantly higher than alteplase [13].</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tenecteplase was associated with significantly better reperfusion (P=0.004) and clinical outcomes than alteplase (P&lt;0.0001) [15].</td>
</tr>
</tbody>
</table>
Thrombolytic Therapy: Tenecteplase

▪ **TEMPO-2**: TNK 0.25 mg/kg vs antiplatelet for minor stroke/TIA in the 0-12hr window (Dec 2023)

▪ **TWIST**: TNK 0.25 mg/kg vs standard of care in 4.5 hrs from onset or from wake up using non-contrast CT and CTA for selection (Dec 2022)

▪ **TIMELESS**: TNK 0.25 mg/kg vs placebo in LVO (MCA/ICA) patients in 4.5 – 24 hr window (April 2022)

▪ **NOR-TEST 2**: TNK 0.4 mg/kg vs alteplase 0.9 mg/kg in 0-4.5 hr or with 4.5 hr from wake-up window (May 2023)
Thrombolytic Therapy: Tenecteplase

- Non-inferior to alteplase
- Superior safety profile
- Easier administration
- Potential for decreased medication errors
- Improvements in door to thrombolytic time

SVIN Registry review of 254,000 global stroke admissions in early months of the pandemic

- 11.5% monthly stroke hospitalizations seen in first months
- 13.2% drop in thrombolytic therapy

Stroke and Covid-19

Raul G. Nogueira, Muhammad M. Qureshi, Mohamad Abdalkader, Sheila Ouriques Martins, et al. on behalf of the SVIN COVID-19 Global Stroke Registry. Neurology Jun 2021, 96 (23) e2824-e2838; DOI:10.1212/WNL.0000000000011885
## Stroke and Covid-19

### Table e-5. Proportion of Patients with COVID-19 and Concomitant Diagnosis of Stroke.

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of Centers</th>
<th>COVID-19 with Any Stroke</th>
<th>Any COVID-19 Hospitalization</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>264*</td>
<td>1,778</td>
<td>119,967</td>
<td>1.48</td>
<td>1.41</td>
</tr>
<tr>
<td>Asia</td>
<td>61</td>
<td>317</td>
<td>20,858</td>
<td>1.52</td>
<td>1.36</td>
</tr>
<tr>
<td>North America</td>
<td>97</td>
<td>615</td>
<td>49,237</td>
<td>1.25</td>
<td>1.16</td>
</tr>
<tr>
<td>Europe</td>
<td>62</td>
<td>507</td>
<td>36,871</td>
<td>1.38</td>
<td>1.27</td>
</tr>
<tr>
<td>South America</td>
<td>27</td>
<td>291</td>
<td>9,865</td>
<td>2.95</td>
<td>2.63</td>
</tr>
<tr>
<td>Oceania</td>
<td>7</td>
<td>1</td>
<td>257</td>
<td>0.39</td>
<td>0.07</td>
</tr>
<tr>
<td>Africa</td>
<td>10</td>
<td>47</td>
<td>2,879</td>
<td>1.63</td>
<td>1.23</td>
</tr>
</tbody>
</table>

*In this analysis of the proportion of patients with COVID and concomitant diagnosis of stroke, 5 centers were excluded due to incomplete COVID-19 hospitalization data.

Stroke and Covid-19

Potential mechanisms:

- Hypercoagulable state (antiphospholipid antibodies, DIC, paradoxical emboli)
- Vasculitis (endothelial dysfunction, cytokine storming)
- Cardiomyopathy (myocarditis, stress cardiomyopathy)

Stroke and Covid-19

Acute Ischemic Stroke
41,971 Patients from 458 Hospitals

With COVID-19
(n=1,143)

- ↑ Non-Hispanic Black, Hispanic, and Asian
- ↑ Large Vessel Occlusion

Diagnostics
- ↑ Door to Brain Imaging Time

Treatment
- ↑ Door to Needle Time
- ↑ Door to EVT Time
- ↔ Intravenous Thrombolytic Use
- ↔ Endovascular Therapy Use
- ↔ GWTG Achievement Measures

Outcomes
- ↑ In-Hospital Mortality
- ↑ Discharge to Skilled Nursing

Without COVID-19
(n=40,828)

- ↑ Age
- ↑ Hypertension
- ↓ Diabetes

↑ Discharge mRS 0-2
↑ Discharge Home
↑ Discharge Inpatient Rehabilitation

Stroke and Covid-19

- Potential prevention and treatment of stroke in COVID-19 patients
  - Ongoing trials for antithrombotic and immunomodulatory drugs
  - Focus on timely revascularization
  - Further investigation into use of telemedicine in stroke assessment
  - Study of association and potential causal relationship between coronavirus and stroke
  - Longitudinal study of long-term disability


Thank you