Stroke: What did we learn in the last year?

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The Year in Acute Stroke

- **Ischemic**
  - Is IV t-PA safe in community practice?
  - Hemicraniectomy for large hemispheric infarction?
  - Rethinking TIA
  - Minocycline as neuroprotectant?

- **Intracerebral hemorrhage**
  - Does recombinant fVIIa improve outcome in non-warfarin ICH?
  - Do statins increase risk of ICH?

Stroke Facts

- 700,000 strokes/year in the U.S.
- 70% of patients survive an acute stroke
- 3,000,000 stroke survivors in the U.S.
- 3rd leading cause of death
- Leading cause of adult disability

Ischemic Stroke - Timeline

0 min
- Embolus Blocks Vessel
- No Symptoms

4-10 min
- Electrical Failure of Neurons
- Clinical Symptoms Begin
- Excitotoxins Released

4 min-hours
- Neuronal Death
- Membrane Breakdown
- Penumbra at Risk

hours-weeks
- Penumbral Region Compensates
- Symptoms Peak 72 hrs
- Rapid Clinical Recovery

2 weeks – 6 months
- Surviving Neurons & Other Hemisphere Compensate
- Logarithmic Recovery
Acute Ischemic Stroke Treatment

- **Reperfusion**
  - Reopening arterial occlusion
  - Improving collateral blood flow

- **Neuroprotection**
  - Stalling “ischemic cascade”

- **“Salvage” Therapy**
  - Managing complications of large stroke

**IV t-PA in ischemic stroke**

**Inclusion Criteria**
- Age ≥ 18
- Clinical diagnosis of acute stroke
- Can initiate treatment within 3 hours of onset of stroke
- head CT without hemorrhage
- More than minor stroke deficit

**Exclusion Criteria**
- complete hemiplegia (very large stroke)
- BP > 185/110 (sustained)
- glucose > 400 or < 50
- platelets <100,000
- INR > 1.7
- recent stroke, trauma, or surgery
- seizure at onset of stroke

**IV t-PA in acute ischemic stroke**

- dose - 0.9 mg/kg IV (maximum 90 mg)
  - 10% as bolus, remainder infused over 1 hour

- must begin treatment w/in 3 hrs of symptom onset

- avoid heparin, ASA, or clopidogrel for 24 hours

- Admit to ICU, keep BP < 185/110 for 24 hours

**Outcome**
- About 1.12 times as many patients treated with t-PA were normal at 3 months compared to placebo
  - t-PA 39% vs. placebo 26%

**Mortality**
- No difference between groups at 3 months
  - t-PA 17% vs. placebo 21%

**Hemorrhage**
- 6.4% of t-PA patients suffered a symptomatic intracranial hemorrhage
- 2.8% of t-PA patients died because of intracranial hemorrhage

*NEJM 333: 1581-1587, 1995*
Barriers to Adoption

- Patients presenting outside time window
  - Most common reason for exclusion
- Safety in “community practice”
  - Major barrier to adoption by ED physicians, general neurologists
  - Addressed by
    - Certifying Primary Stroke Centers (JCAHO)
    - Studying safety and outcome in community settings

SITS-MOST

- Safe Implementation of Thrombolysis in Stroke
  - Monitoring Study (Lancet 2007)
- Observational study of IV t-PA within 3 hours of acute ischemic stroke (2002-2006)
  - 6483 patients
  - 285 centers (50% w/o sig stroke thrombolysis exp)
- Required by European Union regulators

SITS-MOST

- Hemorrhage rate
  - 24 hours - 1.7%
  - 7 days - 7.3%
  - (consistent with 8.6% in pooled randomized trials)
- Mortality
  - 3 months - 11.3%
  - Consistent with 17.3% in randomized trials

SITS-MOST

- Functional outcome – as good or better than randomized trials

Conclusion
- Trial results can be replicated in community practice
- Stop making excuses (my conclusion)
Large Hemispheric Infarction

- Case – 43 yo man with acute complete L MCA ischemic stroke
  - Received IV t-PA w/in 3 hours of onset
  - 12 hours later, deteriorated to deep coma

Options?

1. Let him go
2. ICP monitoring
   - Mannitol, etc
3. Hypothermia
4. Decompressive hemicraniectomy
   - Evidence?

Decompressive Hemicraniectomy

- Allow herniation outwards, not inwards
- “Salvage” therapy not designed to improve deficit from original stroke

Hemicraniectomy

- Considered in
  - “Malignant” MCA infarction
  - Traumatic brain injury
  - ICH, SAH, CSVT

- Difficult to assess efficacy
  - Small trials
  - Sick population
  - Ethical issues
European Pooled Trial Results

- Prospective pooled analysis of 3 ongoing (at the time) trials of decompressive surgery in malignant MCA infarction
- DECIMAL, DESTINY, HAMLET
- Patient criteria
  - Age 18-60
  - Rx w/in 48 hrs of stroke onset
  - Randomized to surgery or conservative Rx
  - 93 patients

Outcome

![Outcome Diagram]

Number Needed to Treat (NNT)

![NNT Table]

Large Hemispheric Infarction

- Hemicraniectomy works
  - Major effect with very low NNT
- Caveats
  - Save lives to a disabled state
  - Many patients & families accept this
  - Study was done on age ≤ 60
  - Don't bias decision based on aphasia (stroke side)
  - Must do wide decompression & durotomy
Rethinking TIA

- Transient Ischemic Attack
  - Focal neurological deficit presumably due to ischemia and resolving completely within 24 hours of onset
- Old way
  - Go home and work up “expeditiously” (often within a week or so)
- New way
  - Treat as “unstable angina” of the brain

Stroke Risk after TIA

- 10.5% risk of stroke w/in 90 days
  - Half of strokes occurred within 2 days
- ABCD² score (points)
  - Age > 60 (1)
  - BP > 140/90 (1)
  - Unilateral weakness (2)
  - Speech impairment without weakness (1)
  - Duration > 60 min (2) or 10-59 min (1)
  - Diabetes (1)

Early Evaluation of TIA

- EXPRESS study - UK (Rothwell et al. Lancet Oct 9, 2007)
- Before/after study of immediate or referral TIA or minor stroke evaluation
  - TIA clinic with evaluation and urgent treatment (rather than referral to primary care)
- 90 day stroke rates
  - Before (clinic referral) 10.3%
  - After (immediate) 2.1%

EXPRESS

- What was done differently?
Early Evaluation of TIA


- 24 hour TIA clinic (seen w/in 4 hrs of presentation)
  - CT or MRI
  - Carotid U/S and or TCD
  - Urgent TTE or TEE if indicated
  - Labs

- Urgent TIA evaluation led to
  - 90 day stroke rate of 1.24%
  - ABCD² predicted rate of 5.96%

SOS-TIA

Panel: Criteria for admission to the stroke unit after assessment in the SOS-TIA clinic

A suspected or identified cause of TIA

- 24 hour TIA clinic
- CT or MRI
- Carotid U/S and or TCD
- Urgent TTE or TEE if indicated
- Labs

New Acute Stroke Trials

- Ischemic Stroke
  - Minocycline as neuroprotectant
  - Clopidogrel loading

- Intracerebral Hemorrhage
  - Recombinant factor VIIa to reduce hematoma expansion

Minocycline in Acute Ischemic Stroke

- Minocycline
  - Anti-inflammatory
  - Matrix metalloproteinase inhibitor
  - Inhibits apoptosis?

- Open-label, evaluator blinded study
- 152 patients
  - 74 minocycline 200 mg/d orally for 5 days
    - Starting 6-24 hours after stroke
  - 77 placebo

Lampl *Neurology* 2007
Minocycline in Acute Ischemic Stroke

Table 2. NIH Stroke Scale (NIHSS), modified Rankin Scale (mRS), and Barthel Index (BI) scores by time of both groups

<table>
<thead>
<tr>
<th></th>
<th>Minocycline treated group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS on admission</td>
<td>7.3 ± 3.2</td>
<td>7.6 ± 3.0</td>
</tr>
<tr>
<td>NIHSS on day 7, mean</td>
<td>6.5 ± 3.0</td>
<td>6.4 ± 4.1</td>
</tr>
<tr>
<td>NIHSS on day 30, mean</td>
<td>5.8 ± 2.1</td>
<td>7.1 ± 4.4</td>
</tr>
<tr>
<td>mRS on admission, mean</td>
<td>1.6 ± 1.9</td>
<td>1.5 ± 1.6</td>
</tr>
<tr>
<td>mRS on day 7, mean</td>
<td>1.3 ± 1.4</td>
<td>1.5 ± 1.3</td>
</tr>
<tr>
<td>mRS on day 30, mean</td>
<td>1.1 ± 1.2</td>
<td>1.2 ± 1.0</td>
</tr>
<tr>
<td>BI on admission, mean</td>
<td>70.0 ± 20.3</td>
<td>63.0 ± 20.4</td>
</tr>
<tr>
<td>BI on day 7, mean</td>
<td>85.9 ± 22.9</td>
<td>85.9 ± 20.8</td>
</tr>
<tr>
<td>BI on day 30, mean</td>
<td>90.0 ± 10.1</td>
<td>90.9 ± 20.6</td>
</tr>
<tr>
<td>BI on day 90, mean</td>
<td>44.0 ± 12.5</td>
<td>77.0 ± 24.0</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic transform (n/N)</td>
<td>5 (6.6)</td>
<td>9 (11.1)</td>
</tr>
</tbody>
</table>

- Differences p < 0.0002 for each of the tests were fixed in NIHSS days 7, 30, and 90, mRS days 7, 30, and 90, and BI days 7, 30, and 90.

- Faster Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence
  - Randomized factorial pilot trial
  - 392 TIA patients within 24 h of symptom onset
  - Clopidogrel
    - 300 mg loading dose then 75 mg daily (v. placebo)
    - Simvastatin 40 mg daily (v. placebo)


FASTER - results

- Trial stopped early due to failure to recruit because of increased use of statins
- 90 day stroke rates
  - Clopidogrel
    - Placebo
    - risk ratio 0.7 [95% CI 0.3-1.2]
  - Simvastatin
    - Placebo
    - risk ratio 1.3 [95% CI 0.7-2.4]

- The interaction between clopidogrel and simvastatin was not significant (p=0.64).

Hematoma Expansion in ICH

- Initial CT
- 10 hours later
Ultra-Early Hemostatic Therapy for ICH

- GOAL: to limit ongoing bleeding and reduce ICH volume in a substantial proportion of patients
- Use as the emergency room counterpart of t-PA for acute ischemic stroke
- Trial agent: Recombinant factor VIIa

NovoSeven ICH Trial

Estimated Mean Percent Change in ICH Volume at 24 Hours

Bars represent 98.3% confidence intervals

Survival at 90 Days According to Study Group

**Modified Rankin Scale at Day 90**

- **160 µg/kg**
- **80 µg/kg**
- **40 µg/kg**
- **Placebo**

**FAST Trial**

- Phase III Trial of rFVIIa in acute ICH
- FAST trial under way globally since May 2005; completed in November 2006
  - >120 global sites; 70 US sites
  - 841 patients randomized; 821 patients dosed
- Largest ICH medical trial ever conducted
- Protocol similar to phase IIb trial
- rFVIIa 80 µg/kg vs 20 µg/kg vs placebo

**FAST: Primary Results**

<table>
<thead>
<tr>
<th>Hematoma Growth at 24 hrs</th>
<th>Placebo</th>
<th>20 µg/kg</th>
<th>80 µg/kg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean % change</td>
<td>26%</td>
<td>18%</td>
<td>11%</td>
<td>0.0004</td>
</tr>
<tr>
<td>Absolute difference</td>
<td>7.8 ± 18.7</td>
<td>4.7 ± 14.8</td>
<td>3.8 ± 15.3</td>
<td>0.009</td>
</tr>
</tbody>
</table>

- Dramatic effect on reducing hematoma expansion
  - Similar to phase IIb study

**Clinical Outcome at 90 days**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>20 µg/kg</th>
<th>80 µg/kg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin Score ≤ 5</td>
<td>24%</td>
<td>26%</td>
<td>29%</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality</td>
<td>19%</td>
<td>18%</td>
<td>21%</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Clinical outcome not affected by treatment
  - Different than phase IIb study

Mayer SA. Presented at the American Academy of Neurology 59th Annual Meeting; April 28-May 5, 2007; Boston, Massachusetts.
FAST: Safety Results

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>20 µg/kg</th>
<th>80 µg/kg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial Thrombotic Events</td>
<td>5%</td>
<td>6%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Cerebral Infarction</td>
<td>0.8%</td>
<td>2.2%</td>
<td>3.2%</td>
<td>0.14</td>
</tr>
</tbody>
</table>

- No difference in
  - Hydrocephalus
  - Venous thromboembolism (e.g. DVT, PE)
- Safety profile similar to phase IIb
- Most MI and cerebral infarctions of limited clinical significance

Mayer SA. Presented at the American Academy of Neurology 59th Annual Meeting; April 28-May 5, 2007; Boston, Massachusetts.

FAST Trial: Conclusions

- Neutral study – no clinical benefit at 90 d
- Dramatic effect on reducing hematoma expansion
- Increase in arterial thrombotic events
- Why different clinical results from phase IIb?

FAST Trial: What Happened?

- Many patients with severe ICH at baseline “unable to be saved”?
  - Elderly, large ICH volume, large IVH volume, poor GCS
- Imbalance in randomization favored placebo
  - Example: IVH in 41% of rVIIa 80 µg/kg, but only 29% in placebo
- Lack of clinical benefit does not seem (on initial analysis) to be a result of arterial thrombotic events
- Subgroup benefit?
  - Example: patients age < 75, treated w/in 3 hrs
    - Beneficial effect of reducing hematoma expansion with rFVIIa irrespective of baseline ICH volume and IVH volume
- Where to go from here?

Do statins cause ICH?

- SPARCL study (NEJM 2006)
  - Randomized trial
  - Atorvastatin 80 mg/d v. placebo

Hazard ratio of 1.66 (95% CI 1.08-2.55) for hemorrhagic stroke

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin treatment</td>
<td>1.4 (1.10, 2.40)</td>
<td>0.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.77 (1.11, 2.81)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age, 10 y increment</td>
<td>1.37 (0.62, 2.99)</td>
<td>0.003</td>
</tr>
<tr>
<td>Entry event – hemorrhagic stroke</td>
<td>6.83 (2.91, 15.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>—</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension (SBP &gt;120 and DBP &gt;80 mmHg)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pre-hypertension (SBP 120-159 or DBP 80-89 mmHg)</td>
<td>3.18 (0.76, 13.34)</td>
<td>0.11</td>
</tr>
<tr>
<td>Stage 1 hypertension (SBP 140-159 or DBP 90-99 mmHg)</td>
<td>3.49 (0.33, 34.63)</td>
<td>0.09</td>
</tr>
<tr>
<td>Stage 2 hypertension (SBP ≥160 or DBP ≥105)</td>
<td>6.19 (1.47, 26.11)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### Interpretation

- Statins probably really do increase the risk of hemorrhagic stroke
- Not clearly an LDL level effect
- Risk of ICH probably offset in patients with ischemic stroke or TIA by benefit in ischemic stroke prevention
- Should ICH patients get high-dose statins (probably not; my view)

The Year in Stroke

- Lots of new information
  - Some good
  - Some not so good
- Central concepts
  - Ischemic stroke
  - Revascularization
  - Treating large hemispheric infarction
  - TIA as a neurologic emergency
  - ICH
  - Hematoma expansion
- Conclusions
  - IV t-PA is part of standard care
  - Hemicraniectomy works
  - ICH remains without a treatment of clinical benefit (but at least a first “disease modifying” approach has been identified)