“Drano for the Braino”: Acute Ischemic Stroke Update

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Disclosures
My Sponsors:

No relevant disclosures
How Common is Stroke?

- Stroke is the 3rd leading cause of death in the US
- In the US, 700,000 strokes occur each year
- Approximately 1 in 4 people die within one year after having an initial stroke
- In the US, approximately 46,000 more women than men have a stroke annually
- The number of people who experience a stroke greatly increases with age

Stroke Is a Major Medical Concern

- Every 45 seconds, someone in the US has a stroke
- Every 3 minutes, someone in the US dies from a stroke. Oregon has 8th highest stroke mortality
- 30% to 50% of stroke survivors do not regain functional independence
- 15% to 30% of all stroke survivors are permanently disabled (ie, not able to walk, talk clearly, or feed themselves with a favored hand)
- Public awareness about the signs of stroke should be improved, so that patients and their loved ones realize when a stroke is occurring

What is Stroke’s Cost to Society?

Total costs: $57.9 billion

Direct costs
• Hospital: $15.5 billion
• Nursing home: $14.3 billion
• Home health care: $3.1 billion

Indirect costs
• Lost productivity/morbidity: $6.4 billion
• Lost productivity/mortality*: $14.2 billion

*Lost future earnings of people who will die in 2006, discounted at 3%.

Overview

• Proposition: Recanalization is good
• Acute recanalization (IV tPA)
  – Intravenous tPA including recent changes
  – Intra-arterial treatments
  – Controversies re: tPA
• Guideline-driven Medical Management
• Malignant MCA stroke
• Random Thoughts
• Questions (and hopefully answers)
Proposition:

Recanalization is Good
Modified Rankin Scale

0--No symptoms.

1--No significant disability. Able to carry out all usual activities, despite some symptoms.

2--Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.

3--Moderate disability. Requires some help, but able to walk unassisted.

4--Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.

5--Severe disability. Requires constant nursing care and attention, bedridden, incontinent.

6--Dead.
NINDS tPA Trial
Outcome at Three Months

Comparison of NIHSS scores at days 1 (pre-tPA), 2, and 3 after tPA in patients who recanalized (blacksquare) vs patients who did not recanalize by MRA or CTA (square)

Linfante, I. et al. Stroke 2002;33:2066-2071
PROACT II (Prolyse in Acute Cerebral Thromboembolism II)

- **Objective:** To determine the clinical efficacy and safety of intra-arterial (IA) recombinant prourokinase (r-proUK) in patients with acute stroke of less than 6 hours’ duration caused by middle cerebral artery (MCA) occlusion.

Furlan et al; *JAMA* 1999; 282: 2003-2011
PROACT II Outcomes

Figure 5. Recanalization of Occluded Middle Cerebral Artery in Patients Treated as Randomized

Furlan et al; *JAMA* 1999; 282: 2003-2011
Table 3. Modified Rankin Scale (mRS) Scores ≤2 at 90-Day Follow-up Assessment*

<table>
<thead>
<tr>
<th>NIHSS Strata</th>
<th>r-proUK Group</th>
<th>Control</th>
<th>Absolute Difference, %</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>mRS ≤2 No. (%)</td>
<td>No.</td>
<td>mRS ≤2 No. (%)</td>
</tr>
<tr>
<td>4-10</td>
<td>16</td>
<td>10 (63)</td>
<td>8</td>
<td>5 (63)</td>
</tr>
<tr>
<td>11-20</td>
<td>75</td>
<td>34 (45)</td>
<td>37</td>
<td>9 (24)</td>
</tr>
<tr>
<td>21-30</td>
<td>30</td>
<td>4 (13)</td>
<td>14</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td>(40)†</td>
<td>59</td>
<td>(25)†</td>
</tr>
</tbody>
</table>

*The upper limit for the 90-day follow-up assessment was prospectively set at 120 days. NIHSS indicates National Institutes of Health Stroke Scale; r-proUK, recombinant prourokinase; mRS, modified Rankin scale; and CI, confidence interval.
†NIHSS stratum adjusted.
‡P = .04 and is based on stratum-adjusted rates.
PROACT II Outcomes

Figure 3. Distribution of NIHSS-Stratum Adjusted Modified Rankin Scores at 90-Day Follow-up Assessment

A score of ≤2 (yellow) on the modified Rankin scale (mRS) indicates a favorable outcome of slight or no disability. A score of 6 represents death. r-proUK indicates recombinant prourokinase.

Furlan et al; *JAMA* 1999; 282: 2003-2011
Does Late Recanalization Help?

A = <1/2 hour
B = 1/2 - 6 hours
C = 6 - 24 hours

Assessed By Doppler

Does Recanalization $\uparrow$ sICH?

**Figure 2**
Proportion of patients with different transcranial Doppler flow findings at the end of IV rt-PA who experienced symptomatic Intracerebral hemorrhage.

- Persistent occlusion: 18 (13%)
- Partial recanalization: 4 (4%)
- Complete recanalization: 4 (3.5%)

$P = 0.005$

Saqqur et al. *Neurology* 2008; 71: 1304-1312
"RECANALISE" Study

Outcome by treatment & site
(Better recanalization IV+IA)
(also < time = better outcome)

Outcome by treatment: mRS ≤2 vs≥ 3
(Depends on recanalization, not Rx)

Mazighi et al: Lancet Neuro 2009; 8:802-809
Conclusions—Formal meta-analysis confirms a strong correlation between recanalization and outcome in acute ischemic stroke. Recanalization is strongly associated with improved functional outcomes and reduced mortality. These findings suggest that recanalization is an appropriate biomarker of therapeutic activity in early phase trials of thrombolytic treatment in acute ischemic stroke.

Rha & Saver: Stroke 2007;38:967-973
How to Accomplish Recanalization
Intravenous tPA, 0.9 mg/kg to a maximum of 90 mg, with 10% as bolus, and the remainder as 1 hour drip is considered standard of care for acute ischemic stroke when treatment can begin within 3 hours of onset (last known normal time) and all inclusion/exclusion criteria are met.

Written consent not necessary though PARQ as with any treatment is required.
tPA Contraindications

*Do NOT administer tPA if any of these statements is true:*

1. Patient's symptoms are **minor** or **rapidly improving**.
2. Patient has had **another stroke or serious head trauma** within the past 3mo.
3. Patient had **major surgery** within the last 14d.
4. Patient has known **history of intracranial hemorrhage**.
5. Patient has **sustained systolic blood pressure >185 mmHg**.
6. Patient has **sustained diastolic blood pressure >110 mmHg**.
7. Aggressive treatment is necessary to lower the patient's blood pressure.
8. Patient has symptoms suggestive of **subarachnoid hemorrhage**.
9. Patient has had **gastrointestinal or urinary tract hemorrhage** within the last 21d.
10. Patient has had **arterial puncture at noncompressible site** within the last 7d.
11. Patient has received **heparin** with the last 48h and has **elevated PTT**.
12. Patient's **prothrombin time (PT)** is >15sec or **INR > 1.7**.
13. Patient's **platelet count** is <100,000/uL.
14. **CT scan hypodensity or acute infarct changes >1/3 MCA territory**

If patient's serum glucose is <50 mg/dL or >400 mg/dL, consider diagnosis.
If patient had seizure at onset of stroke, consider Todd’s before tPA.
Legal Aspects of tPA Use

- 90% of suits to date are for \textbf{NOT} using tPA
- 10% of suits are for complications of tPA
Controversy Persists
Re-Analysis of NINDS trial

- Community Hospitals without neurologists should or should not give tPA for acute stroke?
- NINDS & subsequent studies do or do not adequately demonstrate benefit of IV tPA?
- Trials with larger numbers (e.g. cardiology) are needed assessing IV thrombolysis (no argument)
- IA interventions need neurologic outcomes trials rather than only recanalization trials
Diminishing Benefit of tPA over time
2004 Pooled Analysis (2775 patients)

Figure 3: Model estimating odds ratio for favourable outcome at 3 months in rt-PA-treated patients compared with controls by OTT
Adjusted for age, baseline glucose concentration, baseline NIHSS measurement, baseline diastolic blood pressure, previous hypertension, and interaction between age and baseline NIHSS measurement.
Time Is Brain
### Table 1. Major Inclusion and Exclusion Criteria.

**Main inclusion criteria**
- Acute ischemic stroke
- **Age, 18 to 80 years**
- Onset of stroke symptoms 3 to 4.5 hours before initiation of study-drug administration
- Stroke symptoms present for at least 30 minutes with no significant improvement before treatment

**Main exclusion criteria**
- Intracranial hemorrhage
- Time of symptom onset unknown
- **Symptoms rapidly improving or only minor before start of infusion**
- Severe stroke as assessed clinically (e.g., NIHSS score >25) or by appropriate imaging techniques*
- Seizure at the onset of stroke
- Stroke or serious head trauma within the previous 3 months
- **Combination of previous stroke and diabetes mellitus**
- Administration of heparin within the 48 hours preceding the onset of stroke, with an activated partial-thromboplastin time at presentation exceeding the upper limit of the normal range
- Platelet count of less than 100,000 per cubic millimeter
- Systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg, or aggressive treatment (intravenous medication) necessary to reduce blood pressure to these limits
- Blood glucose less than 50 mg per deciliter or greater than 400 mg per deciliter
- Symptoms suggestive of subarachnoid hemorrhage, even if CT scan was normal
- **Oral anticoagulant treatment**
- Major surgery or severe trauma within the previous 3 months
- Other major disorders associated with an increased risk of bleeding

* A severe stroke as assessed by imaging was defined as a stroke involving more than one third of the middle cerebral-artery territory. NIHSS denotes National Institutes of Health Stroke Scale in which total scores range from 0 to 42, with higher values reflecting more severe cerebral infarcts.
ECASS-III
NNT Analysis

Table 2. Number of Patients Benefited and Harmed Per 100 Patients Treated With Intravenous TPA in Different Time Windows

<table>
<thead>
<tr>
<th></th>
<th>1–3 Hours (NINDS TPA Trials)</th>
<th>3–4.5 Hours (ECASS 3 Trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For transitions across all 7 levels of the mRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefit per 100</td>
<td>32.3</td>
<td>16.4</td>
</tr>
<tr>
<td>Harm per 100</td>
<td>3.3</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Saver et al. STROKE 2009
New 3-4.5 hour Recommendation

“The eligibility criteria for treatment in this time period are similar to those for persons treated at earlier time periods……

**BUT**

all patients receiving an oral anticoagulant are excluded regardless of their international normalized ratio.
Expansion of the Time Window for Treatment of Acute Ischemic Stroke With Intravenous Tissue Plasminogen Activator. A Science Advisory From the American Heart Association/American Stroke Association
Gregory J. del Zoppo, Jeffrey L. Saver, Edward C. Jauch, Harold P. Adams, Jr and on behalf of the American Heart Association Stroke Council
Stroke published online May 28, 2009;
Time Is Still Brain

But you now have 4 ½ hours
Large Vessel Occlusions

- Large vessel stroke is highly morbid
- IV thrombolytics are poorly effective for large vessel stroke
- IA lysis improves clinical outcome (in M1 occlusions)
- Mechanical thrombectomy opens vessels 48-82% of the time and adjuvant IA lysis improves final recanalization to 60-69%
- Better outcome is associated with recanalization
- Randomized data is lacking
- Usually recognized by NIHSS > 10-15 initially
IA Acute Interventions

• Intra-arterial (IA) tPA
  – LKNT 0-6 hrs for anterior circulation
  – <24 hrs for basilar artery occlusion
  – With EKOS Catheter?

• MERCI (Mechanical Embolus Removal in Cerebral Ischemia) or PENUMBRA device
  – LKNT 3-8 hrs with consideration made for >8hrs for compassionate care
  – <24 hours for basilar artery occlusion
  – Used mainly for ICA, Basilar, 1st and 2nd order cerebral arteries

• Intracranial Stent?
Intra-arterial tPA
Concentric Merci® Retriever
Merci V-Series
Penumbra Device
Initial eval & Decision-Making

- ABC’s
- Clinical examination, NIHSS, Swallow
- Labs: CBC, PT, PTT, Chem,
- CT & CTA / PCT if < 6 hours after onset (last known normal) or MRI / MRA / MRP if available
- If tPA eligible and NO large vessel occlusion, give IV tPA.
- If IV tPA eligible with large vessel occlusion, IV tPA followed by intervention or straight to intervention.
- If NOT IV tPA eligible, with large vessel occlusion, go directly to intervention
“Drip and Ship”

• Give usual bolus, start drip, transfer to Referral Hospital with endovascular ability

• IMS III trial: Combined IV tPA and an intra-arterial therapy (IA tPA or mechanical clot removal)
  – tPA dose of 0.6 mg/kg tPA
  – 10% bolus
  – Remainder over 30 minutes
  – Transfer to Referral Hospital
Evidence-based, Guideline-driven Medical Management in Acute Ischemic Stroke (AIS)

- Antithrombotic
- DVT Prophylaxis
- Fluids & Nutrition
- Temperature
- Glucose
- Blood Pressure
- Arrhythmia
Acute Anticoagulation

Heparin/ warfarin: Classically used for all strokes

- IST trial: Heparin vs ASA: 20,000 stroke patients
  Heparin: 12 %; ASA 12 % rate of recurrent CVA/death

- TOAST trial: ORG 10172 vs placebo: 1200 stroke patients
  No difference in stroke progression or recurrence
  Increases risk of hemorrhagic conversion (3 X).

- WARS Trial: ASA vs warfarin: Trend for ASA

Anticoagulation not recommended for acute stroke treatment
Aspirin is only proven acute antithrombotic

Exceptions: Dissection, Venous sinus thrombosis
Antithrombotic in AIS

- Administer ASA 325 mg po/pr daily if NOT using tPA. Can start 24 hours after tPA.
- Other regimens such as clopidogrel load are currently under investigation (FAST trial, POINT trial). Many now give clopidogrel 450-600 mg load in specific instances (level III evidence).
DVT Prophylaxis in ICH

• DVT Prophylaxis is standard of care in all patients not ambulating.
  – Mechanical: SCDS, TEDS alone not effective.
  – Pharmacological:
    • LMWH (usually preferred)
    • SQ Heparin (HIT risk)

• Do not use LMWH/heparin for 24 hours after tPA.
Fluids & Nutrition

• Use isotonic, non-glucose-containing fluids (0.9% NaCl) at ~1ml/kg/hr if euglycemic.

• As with all neurocritically ill patients, enteral nutrition should be started within 48 hours to avoid malnutrition.
Temperature

• Sustained fever (>38.3°C) is independently associated with poor outcomes. However, evidence that control improves outcome is meager at best.

• Consensus is that euthermia (≤ 37.5°C) should be maintained with acetaminophen and external cooling devices.
Glucose

- Maintain euglycemia as with other critically ill patients (< 140 or 150)
- Evidence shows correlation between poorer outcomes and hyperglycemia
- But no evidence yet shows that correcting hyperglycemia results in better outcome.
Blood Pressure

Do NOT Over-treat in first week

- t-PA limit 185/110 mm/Hg
- If NO tPA, Lower BP by 15% if exceeds 220/120 mm/Hg
- Choice of BP agent is controversial: labetolol, nicardipine & clevidipine do not raise ICP
- ?? Keep patients flat for initial period??
Malignant MCA Stroke

Destiny, Decimal, Hamlet Trials

Inclusion criteria for hemicraniectomy within 48 hours of onset

Age 18–60 years Clinical deficits suggestive of infarction in the territory of the MCA with a score on the National Institutes of Health stroke scale (NIHSS) >15

Decrease in the level of consciousness to a score of 1 or greater on item 1a of the NIHSS

Signs on CT of an infarct of at least 50% of the MCA territory, with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or infarct volume >145 cm$^3$ as shown on diffusion weighted MRI

Hemicraniectomy

Hemicraniectomy

In conclusion, decompressive surgery increases the probability of survival without increasing the number of very severely disabled survivors. Still, the decision to perform decompressive surgery should be made on an individual basis in every patient.

Brain Edema

- Posterior fossae strokes should be treated with suboccipital decompression if brainstem is compressed
- Hemicraniectomy for hemispheric stroke is proven to reduce morality and improve outcomes in appropriate patients (Level 1 evidence)
- Mannitol, hypertonic saline, and hyperventilation are not validated but are important bridges to surgical interventions as necessary
- Follow Na⁺
- No indication for corticosteroids
Random Thoughts

• Initiate secondary prevention measures while hospitalized for stroke
  – Improved long-term compliance (PROTECT)
  – Antithrombotic choice (PROFESS)
  – Lipid lowering (SPARCL, JUPITER)
  – Smoking cessation
  – Other: ACEI, ARB, diuretic, lifestyle, etc
• Prolonged Asymptomatic Event Monitoring for AF
• Possible Role of BNP in acute stroke for AF
• Possible Future Treatments
  – Combined Fibrinolytics And Glycoprotein IIb/IIIa Antagonists
  – Treatment based on physiologic indicators (Mismatch on MRI)
  – Albumin, perfusion enhancement, Neuroprotectants
Arrhythmia-right insula

- Cerebrogenic Sudden Death
- QT Prolongation
- Late ventricular potentials
- Frequent PVC’s
- Polymorphic PVC’s
- R-on-T phenomenon
- Runs of V tach
- Abnormal heart rate variability
*Stroke CT = CT + CTA
Summary

- Collaboration in AIS is a key to success
- Recanalization is important
- IV tPA is current standard of care at 0-3 hrs.
- New ASA Guideline: IV tPA from 3-4.5 hrs.
- IA therapies for large artery occlusion may give better outcomes than IV tPA
- Proper medical management is a key to success
- Consider hemicraniectomy in malignant MCA infarcts
- Despite 14 years of IV tPA, controversy persists
Thank you for
Your kind attention