Acute Ischemic Stroke
A Practical Approach to Management
and an Ounce of Prevention

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Cardinal Symptoms of Stroke

Ischemic Stroke Causes

Goals of Therapy in AIS
1. Reduce early mortality
2. Limit infarct size
3. Prevent early recurrence
4. Reduce level of disability in long-term survivors
5. Prevent / limit complications
6. Prevent late recurrence

PL’s BIG 9 Acute Stroke Issues
1. Acute Stroke-Specific Therapies
2. Acute Hypertension
3. Hyperthermia
4. Hyperglycemia
5. Fluid/Electrolyte disturbances
6. DVT/PE prevention
7. Seizures
8. Elevated intracranial pressure
9. Hemorragic transformation

Acute Stroke-Specific Therapy
Antithrombotic Therapy

ASA in AIS - CAST+IST+MAST-I
Aspirin 160 or 300 mg/d starting <48h post AIS, x 2-4 weeks

During scheduled treatment

Heparin in AIS - International Stroke Trial
- Design: RCT, open label
- Population: 19,331 with AIS
- Intervention: Heparin 5,000U SC bid x 14d vs. Avoid Heparin

"Aspirin should be given within 24-48 hours of stroke onset in most patients"

"Urgent Anticoagulation"
- Commonly used
  - Presumed cardioembolic stroke
  - Early recurrence: 0.3-0.5% per day
  - Contraindicated within 24h of tPA
- Cochrane Review 2003:
  - N=16,558, UFH/LMWH vs. ASA
  - OR Death=1.10, OR ICH=2.35
- RAPID Trial: adjusted-dose UFH vs. ASA within 12h of onset in non-lacunar strokes
- Routine use not recommended. In particular, not recommended in moderate-severe stroke.
  (ASA Guidelines 2003)

LMWH, heparinoids, etc.
- TOAST (Danaparoid vs. placebo) - No improved outcomes, more serious ICH.
- HAMST (Dalteparin vs. ASA in AIS with AF) - no differences in efficacy or safety - too small to conclude anything.
- TOPAS (Cetiparin vs. placebo) - not effective
- TAIST (Tinzaparin vs. ASA) - Similar efficacy, more bleeding with tinzaparin.
- FISS (Nadroparin vs. placebo) - RR poor outcome @ 6mos 0.54 with nadroparin 4100 SC bid
- STAT (Ancrod x 72h within 3h of onset vs. placebo) - improved outcomes, more symptomatic ICH.
- ESTAT (Ancrod x 72h within 6h of onset vs. placebo) - increased 90d mortality
Other Antithrombotics

- AbESTT (Abciximab within 6h vs. placebo) - 3.5% vs. 1% symptomatic ICH. Improved mortality & outcomes?
- ABEST II
- ARGIS-I (Argatroban within 12h vs. placebo) - no difference in efficacy or safety.
- ROSE - reteplase + abciximab vs. placebo

Thrombolysis

NINDS tPA Trial
- Design: RCT, open label
- Population: 333 with AIS
- Intervention: tPA 0.9 mg/kg or placebo over 60 mins within 3h of onset

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<tr>
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<th>tPA</th>
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<td>tPA</td>
<td>53/158</td>
<td>76/158</td>
<td>23%</td>
<td>0.37</td>
<td>9</td>
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<tr>
<td>Placebo</td>
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| Effects of time to treatment for favourable outcome @3 mos (tPA vs. Placebo)

Symptomatic ICH with tPA within 7-10 days of treatment

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<td>17/158</td>
<td>10/158</td>
<td>70%</td>
<td>3.06</td>
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<tr>
<td>Placebo</td>
<td>10/158</td>
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<td>0%</td>
<td>1.00</td>
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NINDS tPA Trial
- Effects of time to treatment

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Thrombolysis Contraindications

Thrombolytic therapy cannot be recommended for persons excluded from the NINDS Study for one of the following reasons:
1. Current use of oral anticoagulants or INR > 1.5;
2. Use of heparin in the previous 48 hours and a prolonged partial thromboplastin time;
3. Platelet count < 10,000/mm3;
4. Major surgery within the preceding 14 days;
5. Pretreatment systolic blood pressure greater than 185 mm Hg or diastolic blood pressure greater than 110 mm Hg;
6. Rapidly improving neurological deficits;
7. Isolated, mild neurological deficits, such as ataxia alone, sensory loss alone, dysarthria alone, or minimal weakness;
8. Prior intracranial hemorrhage;
9. Blood glucose less than 50 mg/dL (2.7 mmol/L);
10. Seizure at the onset of stroke (Todd’s paralysis may mimic stroke and/or make neurologic evaluation difficult);
11. Gastrintestinal or urinary bleeding within the preceding 21 days;
12. Recent myocardial infarction;
13. Treatment > 3h from onset of symptoms;
14. Arterial puncture at non-compressible site within 7 days

TPA proponents:
AHA (ASA)
AAN
Canadian Stroke Consortium
European Stroke Initiative

TPA opponents:
CAEP
AAEM
ACEP
Unlicensed in Australia

“Neuroprotective” Therapy

Acute Hypertension

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<th>BP</th>
<th>Treatment</th>
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<tr>
<td>SBP &lt; 140</td>
<td>Monitor BP q30 minutes x 2 hours, then q60 minutes x 6 hours, then q4 hours x 16 hours.</td>
</tr>
<tr>
<td>SBP 140-180</td>
<td>Nil.</td>
</tr>
<tr>
<td>SBP 180-200 or DBP 120-140</td>
<td>10 mg labetalol IV push over 1-2 minutes. May repeat or double dose every 10 minutes to max 180 mg, or give the initial labetalol bolus and start labetalol drip at 2 mg/min.</td>
</tr>
<tr>
<td>SBP &gt; 200 or DBP &gt; 140</td>
<td>If BP not controlled by labetalol, consider nitroprusside.</td>
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Blood Pressure Lowering in AIS

- Low initial BP associated with GOOD and BAD outcomes.
- High initial BP associated with GOOD and BAD outcomes.
- INWEST nimodipine trial (1994)
- Oliveira-Filho 2003:
  - N=115 AIS patients, mean BP 160/94
  - all had BP drop in first 24h, 59% received antihypertensives
  - at 3 months only predictor of poor outcome was higher NIHSS and degree of BP reduction in first 24h
  - OR of poor outcome per 10% drop in BP: 1.89

INWEST. Cerebrovasc Dis 1994;4:204-10

ACCESS: Candesartan in AIS

**Design:** RCT, double-blind

**Population:** 342 AIS patients with BP >200/110 within 6-12h, or BP >180/105 24-36h after admission.

**Intervention:** PHASE 1: Candesartan 4mg or placebo x 7 days. PHASE 2: Candesartan + other antihypertensives in anyone who was still hypertensive.

**Duration:** 7 days for PHASE 1. 1 year for PHASE 2.

**Outcomes:** Mortality, Disability (Barthel) @ 30d. Mortality + Stroke + ACS at 1 year.

ACCESS. Stroke 2003;34:1699-1703.

DVT/PE Prophylaxis

- PE causes 10% of deaths in AIS
- advanced age, immobility, atrial fibrillation, lower extremity paralysis
- PE in IST @ 14d: heparin 0.5%, no heparin 0.8% (NNT=334)
- What about ASA?
  - no effect on PE in IST+CAST (0.1 vs 0.2%)
  - VTE in PEP Trial: ASA 160mg/d 1.6% vs. 2.5% (NNT=112)


Efficacy of Antithrombotics for DVT/PE Prophylaxis in AIS
Fluid/Electrolyte Disturbances

- SIADH: 10-14% incidence
- Diabetes Insipidus: Incidence?
- Avoid “free-water” containing crystalloids

Hyperthermia following AIS

- Mortality OR 1.19
- Based on Temp >37.5°C within first 24h
- Use antipyretics to maintain normothermia, particularly during first 24h post-stroke
- Induced Hypothermia?

Hyperglycemia following AIS

- Atherothrombotic, cardioembolic, undetermined strokes
- Lacunar strokes

Hajat et al. Stroke 2000;31:410-4
Bruno et al. (TTAIST Trial data). Neurology 1999;52:280-4

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Hyperglycemia following AIS

- Elevated Hgb A1C NOT associated with worse outcomes
- No evidence of efficacy of lowering BG in AIS
- "By consensus, a reasonable goal would be to lower markedly elevated glucose levels to 300 mg/dL (16.63 mmol/L) (grade C)"


Brain Edema / Elevated ICP

- 5-20% incidence
- Peaks 3-5 days post-stroke
- Management:
  - Avoid hypotonic fluids
  - Avoid antihypertensives
  - Furosemide 40 mg IV
  - Mannitol 0.25-0.5 g/kg IV over 4h q6h PRN
  - Hyperventilation, surgery, CSF drainage
- No evidence of improved outcomes with any of these measures

Hemorrhagic Transformation

- 5-30% incidence
- Parenchymal hemorrhage vs. Hemorrhagic infarction
- Petechiae vs. Hematoma
- Symptomatic vs. Asymptomatic
- CAST+IST meta-analysis:
  - ASA 1% vs. Placebo 0.8% (NS)
  - Effects of SC heparinoids?

Seizures
Seizures following AIS

- 3-43% incidence
- over 9 months, 8.6% in ischemic stroke vs. 10.6% in hemorrhagic
- 27% develop epilepsy
- 78% occur in first 24h
- Usually PARTIAL (+/- secondary generalization)
- probably do not influence overall prognosis
- Usual principles of seizure management


Other Issues

- Aspiration
- Dysphagia
- Neuropathic pain, movement disorders
- Depression
  - N=104 with AIS, RCT double-blind
  - nortriptyline or fluoxetine vs. placebo x 12 weeks beginning ~2 weeks post-stroke
  - Mortality @ 9 years: 67.9% vs. 35.7% (NNT=4)


Hot Stroke Prevention Stuff

TOAST ASA Pretreatment Data

N=509 ASA users, 766 non-users within 1 week of stroke

NIH Stroke Scale at Time of Stroke

Wilkensdink et al. Stroke 2001;32:2835-41

Stroke risk with chronic Atrial Fibrillation

"CHADS2"

- LV Dysfunction (CHF)
- HTN
- Age > 75
- Diabetes
- Previous Stroke/TIA
- Atrial Enlargement (+40mm)
- Thrombus in L atrial appendage
- Peripheral Embolism

Gage et al. JAMA 2001;285:2864-7

Primary Prevention

Estimating benefits/risks of therapy in AF

- CASE: 78 y/o with AF, diabetes and recent TIA

Primary Prevention

Loewen & Sprague. AJHP 2003;60:427-9
Effectiveness of Warfarin in AF

- Cohort study, N=11,526 with AF, mean 71 y/o
- 2.2 years of observation

Rate per 100 person-years

Go et al. JAMA 2003;290:2885-92