Case 1

- A 58 year-old woman with no past medical history presented to the ED after the sudden onset of aphasia and right sided weakness.
- Exam shows a mild expressive aphasia, R face and arm weakness as well as L gaze deviation.
- Her symptoms began at 3 p.m., it is now 6:30 p.m.
What treatment should you initiate?

A. IV t-PA
B. IV heparin
C. Antiplatelets
D. Mechanical Embolectomy
E. Intra-arterial t-PA

The 2013 Acute Stroke Timeline

- Time of onset = last time seen normal
  - 0-4.5 Hours    IV-tPA
  - 0-6 Hours      IA-tPA
  - 0-8 Hours      Mechanical Embolectomy
  - Greater than 8 hours   Anticoagulants or Antiplatelets
Intravenous t-PA: Proven, Approved

• Pivotal IV t-PA NINDS trial (0-3 hours)
  – 30% increase in minimal or no disability at 90 days, not the Lazarus effect
  – Symptomatic hemorrhage risk increased 0.6 to 6.4%, half were serious and fatal
  – No change in mortality
  – Multiple recent studies confirm this result in diverse settings
  – THE EARLIER THE BETTER!!!
Intravenous t-PA: 3-4.5 hours

- ECASS III trial (9/08)
  - 821 pts randomized to t-PA vs placebo
  - Median time: 3h 59min
  - Favorable outcome: 52% vs 45%, p=0.04
  - Symptomatic ICH: 2.4% vs 0.2%, p=0.008
  - No mortality difference


Future Directions

- Perfusion-Based Time Window

- Ultrasound-enhanced thrombolysis
  - With IV t-PA in 4.5 hour window

- More Neuroprotectant trials: ALIAS, Fast-MAG

- Combination Approaches: IMSIII
Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke


<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Relative Risk (95% CI)</th>
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<tbody>
<tr>
<td>NINDS score</td>
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<tr>
<td>0–19</td>
<td>452</td>
<td>1.01 (0.79–1.26)</td>
</tr>
<tr>
<td>20–29</td>
<td>254</td>
<td>1.37 (0.85–2.20)</td>
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<tr>
<td>Age</td>
<td></td>
<td></td>
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<tr>
<td>18–65 yr</td>
<td>276</td>
<td>1.07 (0.78–1.48)</td>
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<tr>
<td>&gt;65 yr</td>
<td>204</td>
<td>1.04 (0.69–1.55)</td>
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<tr>
<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>556</td>
<td>0.99 (0.62–1.63)</td>
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<tr>
<td>Male</td>
<td>340</td>
<td>1.16 (0.70–1.93)</td>
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<tr>
<td>Atrial fibrillation</td>
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<td></td>
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<tr>
<td>No or unknown</td>
<td>433</td>
<td>1.13 (0.64–2.02)</td>
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<tr>
<td>Yes</td>
<td>223</td>
<td>0.89 (0.50–1.63)</td>
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<tr>
<td>Stroke onset to intravenous t-PA ≤120 min</td>
<td>345</td>
<td>1.24 (0.88–1.74)</td>
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<tr>
<td>&gt;120 min</td>
<td>310</td>
<td>0.88 (0.62–1.26)</td>
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<tr>
<td>ASPECTS</td>
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<td></td>
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<tr>
<td>0–7</td>
<td>271</td>
<td>1.18 (0.67–1.87)</td>
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<tr>
<td>8–10</td>
<td>378</td>
<td>1.01 (0.79–1.34)</td>
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<tr>
<td>ICA, M1, or basilar occlusion</td>
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<td>1.05 (0.67–1.64)</td>
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<tr>
<td>NINDS score 2–19</td>
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<tr>
<td>Stroke onset to intravenous t-PA ≤120 min</td>
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<td>1.16 (0.83–1.64)</td>
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<td>&gt;120 min</td>
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<td>0.88 (0.62–1.29)</td>
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<td>Stroke onset to intravenous t-PA ≤120 min</td>
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<td>&gt;120 min</td>
<td>89</td>
<td>0.98 (0.28–3.39)</td>
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<tr>
<td>ICA, M1, or basilar occlusion</td>
<td>324</td>
<td>1.18 (0.66–2.10)</td>
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<tr>
<td>Stroke onset to intravenous t-PA ≤120 min</td>
<td>98</td>
<td>0.89 (0.42–1.87)</td>
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</table>
Future Directions

• Perfusion-Based Time Window

• Ultrasound-enhanced thrombolysis
  – With IV t-PA in 4.5 hour window
• More Neuroprotectant trials: ALIAS, Fast-MAG
• Combination Approaches: IMSIII
• Much improved endovascular devices with recanalization rates approaching 90%

Case 2

• A 78 year-old man with a history of DM, HTN presents with 2 days of R arm weakness
• Examination shows a mild R facial droop sparing the forehead as well as a R pronator drift and slowed, clumsy movements in the R hand
• The patient is on aspirin, lisinopril, and metformin
Which of the following is not part of the standard stroke workup?

A. Echocardiogram
B. Extended cardiac telemetry
C. Lipid panel
D. B12, TSH, RPR, ESR
E. Carotid evaluation

Standard Large-Vessel Stroke Workup

• Cardioembolic: afib, clot in heart, paradoxical embolus
  • 1. Telemetry
  • 2. TEE with bubble study
• Aortic Arch
  • 2. TEE with bubble study
• Carotids
  • 3. Carotid Imaging (CTA, US, MRA, angio)
• Intracranial Vessels
  • 4. Intracranial Imaging (CTA, MRA, angio)

And evaluate stroke risk factors
**TEE vs. TTE**

- 231 consecutive TIA and stroke patients of unknown etiology underwent TTE and TEE
- 127 found to have a cardiac cause of emboli, 90 of which (71 percent) only seen on TEE
- 38 of 46 “major risk factors” only found on TEE (most left atrial thrombi)
- TEE superior to TTE for: LA appendage, R to L shunt, examination of aortic arch

Atrial Fibrillation Detection

- EKG
- 48 Hours of Telemetry
- 30 day cardiac event monitor
  - 20% of patients with cryptogenic stroke otherwise unexplained had afib detected
  - Clearly changes management
  - Probably cost effective

Kamel H et al: *Stroke* 41:1514, 2010

Do These Episodes of AF Really Matter?

**Subclinical Atrial Fibrillation and the Risk of Stroke**

Jeff S. Healey, M.D., Stuart J. Connolly, M.D., Michael R. Gold, M.D.,
Carsten W. Israel, M.D., Isabelle C. Van Gelder, M.D.,
Alessandro Capucci, M.D., C.P. Lau, M.D., Eric Fain, M.D., Sean Yang, M.Sc.,
Christophe Baillieul, M.D., Carlos A. Morillo, M.D., Mark Carlson, M.D.,
Ellison Theelemes, M.Sc., Elizabeth S. Kaufman, M.D.,
and Stefan H. Hohnloser, M.D., for the ASSERT Investigators®

Silent AF and Its Consequences

- Examined patients >65 years old with HTN
- All had pacemaker placed 8 weeks prior
- Interrogated pacer for AF over 3 months
  - 261/2451 (10%) patients with at least 1 episode defined as greater than 6 minutes in length
    - All but 7 were completely subclinical
    - Median time to detection was 35 days

Silent AF and Its Consequences

- Patients were then followed for 2.5 years
  - Compared to those without AF in the first 3 months, those who did had significantly higher rate of systemic embolism or stroke
    - HR 2.49; 95% CI, 1.28 to 4.85, P=0.007
- No difference adjusted for vasc. risk factors
- No difference if episode that was detected lasted 6 minutes, 6 hours, or 24 hours
Approach to Stroke Treatment

Acute Stroke Therapy?
- No

Anticoagulants?
- No

Antiplatelets

Shrinking Indications for Anticoagulation in Stroke

1. Atrial Fibrillation
2. Some other cardioembolic sources
   - Thrombus seen in heart
   - ?EF<35  WARCEF 2012
   - ?PFO with associated Atrial Septal Aneurysm
3. ?Vertebral dissection
   - 2009: Questionable in carotid dissection
4. Rare hypercoagulable states: APLA

3 New Trials!
Case 3

• A 60 year-old man with a history of DM, smoking presents 10 hours after the onset of slurred speech and right arm and leg weakness.
• The patient is on ASA 81mg daily

Stroke workup is unrevealing.
Your Treatment?

A. Increase ASA to 325mg daily
B. Add Plavix
C. Stop ASA, start Plavix
D. Anticoagulate
E. Stop ASA, start Aggrenox
Approach to Stroke Treatment

Acute Stroke Therapy?
  ↓ No
Anticoagulants?
  ↓ No
Antiplatelets

Antiplatelet Options

• 1. ASA
  – 50mg to 1.5g equal efficacy long-term
• 2. Aggrenox
  – 25mg ASA/200mg ER Dipyridamole
    • ESPS-2, ESPRIT (Lancet 5/06)
• 3. Clopidogrel (Plavix)
  • MATCH (Lancet 7/04)
  • FASTER (Lancet Neurol 10/07)
PRoFESS Trial

- Randomized, double-blind trial of Aggrenox versus Plavix in over 20,000 patients with ischemic stroke
- Recurrent 4-year event rates basically identical between the two medications
  - HR for Aggrenox 1.01 (95% CI, 0.92-1.11)
  - Composite of stroke, MI, vascular death: 13.1% in each
  - Major hemorrhagic events higher in Aggrenox group


Clopidogrel + ASA: Ever A Winning Combination?

- Randomized, double-blind trial in over 3000 patients with lacunar stroke
  - ASA+placebo vs. ASA+Clopidogrel
- Mean follow up of 3.4 years
  - Risk of recurrent stroke was 2.7% per year vs. 2.5% (HR 0.92, 95% CI 0.72-1.16)
  - No difference in rates of ischemic stroke or fatal/disabling stroke
  - Risk of major hemorrhage was doubled in the dual antiplatelet group

Antiplatelet Options

- If on no antiplatelet medication
  - Plavix vs. Aggrenox (or ASA)
- If already on ASA
  - Switch to Plavix vs. Aggrenox
- If already on Plavix or Aggrenox
  - ???
- Never use combinations except in fresh stents and in ultra-early ongoing trials

Other Acute Stroke Management

- Statins for (almost) all
  - SPARCL (NEJM 8/06), 80mg atorvastatin in stroke and TIA if LDL>100
- Tight Glucose and Fever control
- Enoxaparin for DVT prophylaxis
  - PREVAIL trial (Lancet 2007)
  - CLOTS trial 1 (Lancet 2009): Compression Stockings
Permissive Hypertension

• National Guidelines
  – To at least 220/120: Morbidity increases if lower in the acute setting
  – After IV tPA: less than 185 systolic for 24 hours
• Randomized trial of 2020 patients with acute stroke: candesartan vs placebo for 7d
  – Lower pressures with candesartan
  – No benefit to treatment
  – Higher risk of poor functional outcome with candesartan


Permissive Hypertension

• When to stop remains controversial
• Situations where more important
  – Large Vessel Occlusion
  – Fluctuating Symptoms
• We begin a medicine before discharge (~72h) and aim for normotension over a matter of weeks
  – Choose thiazides and ACEI first
Case 4

• A 72 year-old woman with HTN comes to the ED after a 5 minute episode of aphasia and right arm weakness that has since resolved.
• Exam is normal except blood pressure is 175/40

What would be your triage?

A. Admit to the hospital floor
B. Admit to the ICU
C. Send home and f/u with PCP in 1-2 weeks
D. Send home with f/u the next day
E. No f/u required
TIA versus Stroke

• Up to 50% of TIA have infarct on imaging
• Conceptually the same disorder
  – Same workup, same treatment
• Pendulum swing
  – Pre-2001: Much more aggressive with Stroke
  – 2002-2007: TIA and Stroke equally aggressive
  – 2008-present: Moving to more aggressive approach with TIA

Risk of Future Stroke with TIA: ABCD² Score

• 7-day risk overall 8.6-10.5 percent
• Age
  – >60 =1 point
• Blood Pressure
  – SBP>140 or DBP>90 =1 point
• Clinical Features
  – Unilateral weakness =2 points
  – Speech disturbance without weakness =1 point
• Duration
  – >60 minutes =2 points
  – 10-59 minutes =1 point
• Diabetes=1 point

Aggressive Therapy for TIA

• 1. SOS-TIA trial
  – 1085 patients with TIA admitted to a 24-hour center
  – All treated with standard therapy
    • 74 percent discharged on same day, stroke risk reduced 80 percent from ABCD² prediction
• 2. EXPRESS study
  – 80 percent reduction in risk with urgent TIA clinic visit versus usual primary care visit in 1278 patients


When to Fix the Carotid?

• NASCET in early 1990s
  – Benefit of endarterectomy in patients with symptoms ipsilateral to 70-99% stenosis
    • Comparison: best medical management at the time
  – 50-69% symptomatic stenosis revascularization has limited benefit, especially in women
• In stroke management don’t miss carotid disease or atrial fibrillation
How to Fix the Carotid?

• Stenting +/- distal protection
  – SAPPHIRE (NEJM 10/04 and 4/08) in high-risk patients as good as endarterectomy
  – Currently widely practiced: NeuroIR, vascular surgeons, BodyIR, Cardiologists
  – Unique risks: Hypotension, Bradycardia

CREST Trial Results

• 4-year study of 1321 symptomatic and 1181 asymptomatic patients randomized to CEA or carotid stenting
• Combined endpoint of stroke, MI, death not significantly different
  – More strokes in first 90 days in stenting group, more MIs in surgical group
  – After 90 days, similar endpoints