Case 1

• A 70 year-old man with no past medical history presented to the ED after the sudden onset of left sided weakness.
• Exam shows normal language, L face and arm weakness as well as R gaze deviation.
• He was last seen well at 3 p.m., it is now 6:45 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 2014 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!!!

Meta-analysis of all major t-PA trials of patients treated within 3 hours
mRS 0–2, 365/896 [40·7%] vs 280/883 [31·7%]
Odds Ratio: 1·53, 1·26–1·86, p<0·0001
Absolute Benefit: 90 per 1000 people treated

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


Speed Matters:
Time is Brain

- Examination of the Get With the Guideline Registry in the U.S. over the last decade
  - 1400 hospitals, nearly 59,000 patients
  - Mean time to treatment was 144 minutes
    - Earlier on weekdays, more severe stroke, arrival in ambulance
- For every 15 min earlier administration...
  - Significantly lower in-house mortality
  - Significantly lower rates of ICH
  - Significantly more independent ambulation at d/c
  - Significantly higher rate of d/c to home

Future Directions

• Perfusion-Based Time Window

• Ultrasound-enhanced thrombolysis
  – With IV t-PA in 4.5 hour window
• Combination Approaches: IMSIII

IMS III Trial:
The Death of Interventional Strategies?

• Randomized patients to IV t-PA alone within 3 hours versus IV t-PA followed by possible endovascular treatment
  – Flexible study design
• Stopped early after ~650 patients enrolled since absolutely no effect seen
  – No efficacy differences
  – No safety differences

What to do now regarding these endovascular therapies?

• 1. Continue to use them in patients who are ineligible for IV t-PA
• 2. Should probably not use following IV t-PA administration unless part of a randomized trial of the newer-generation devices
  – Rather focus systems-based efforts on speeding up the administration of IV t-PA
• 3. Basilar lesions are an important exception as they were not part of any of these trials

Case 2

• A 63 year-old man with a history of HTN and smoking presents with 3 days of R arm weakness
• Examination shows a mild R facial droop that spares the forehead as well as a R pronator drift and slowed movements of the R hand
• The patient takes aspirin and HCTZ
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
  – 15-20% of patients with cryptogenic stroke otherwise unexplained had afib detected
  – Clearly changes management
  – Probably cost effective


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
   - PFO with associated Atrial Septal Aneurysm
3. Vertebral dissection
   - 2009: Questionable in carotid dissection
4. Rare hypercoagulable states: APLA

Heparin in Acute Stroke

- Recent study looked at the 5 largest trials of heparin, heparinoids, LMWH in acute stroke
- Could find no benefit even in those patients with highest risk of recurrent ischemia and lowest risk of hemorrhage
- Considering use of heparin for “selected patients” therefore seems unwise

The Excitement Over the Demise of Warfarin

• Oral direct thrombin and Xa inhibitors will hopefully lead to more patients with afib being anticoagulated
• Stroke-specific concerns
  – Little acute data for secondary prevention
  – Contraindications to tPA
  – Reversal

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 to ASA  
C. Stop ASA, start Plavix  
D. Stop ASA, start Aggrenox  
E. Anticoagulate

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

- **3. Clopidogrel (Plavix)**
  - Multiple secondary prevention studies (CHARISMA, SPS3) show no benefit in combination with ASA

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

**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
  - ???

**Clopidogrel + ASA: Ever A Winning Combination?**

- CHANCE trial
  - 5170 TIA or Minor Stroke patients assigned to daily ASA + Placebo versus daily ASA + Clopidogrel following 300mg load
  - Primary outcome was stroke at 90 days
    - NNT=29 to prevent 1 stroke
    - Similar safety endpoints
- Generalizability?
  - Await POINT trial results

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
  – 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
• We typically stop all meds except half-dose β-blockers

CATIS Trial

• Over 2000 patients in China randomized within 48 hours of stroke to…
  – 1. HTN treatment to lower bp by 10-25% in the first 24 hours after randomization, with goal <140/90 mmHg within 7 days
  – 2. Stop all anti-HTN meds during hospitalization (control)

• Primary end point: Likelihood of death and major disability at 14d or at discharge


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 69 year-old man with HTN comes to the ED after a 5 minute episode of right arm weakness that has since resolved.
• Exam is normal except blood pressure is elevated at 163/92

Other than TIA, what is the most common neurologic diagnosis here?
A. Conversion disorder
B. Migraine
C. Focal Seizure
D. UTI
E. Cervical spine lesion
TIA versus Stroke

• Up to 30-50% of TIA have infarct on MRI
• 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: A more aggressive approach with TIA outside of the acute treatment window

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
  – Became 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