Advances in Prevention and Treatment of Stroke:
What Every Primary Care Clinician Needs to Know

S. Andrew Josephson MD
Carmen Castro Franceschi and Gladyne K. Mitchell Neurohospitalist Distinguished Professor
Chair, Department of Neurology
Director, Neurohospitalist Program
University of California, San Francisco

The speaker has no disclosures.

Case 1

- A 65 year-old right handed woman with a history of HTN and DM presented to the ED after the sudden onset of right sided weakness.
- Exam shows mild expressive aphasia, R face and arm weakness as well as L gaze deviation.
- She was last seen normal at 1 p.m., and it is now 2:45 pm

The 2017 Acute Stroke Timeline

- Time of onset = last time seen normal
- 0-4.5 Hours IV-tPA
- 0-6* Hours Mechanical Embolectomy
- Greater than 6* hours Anticoagulants or Antiplatelets

*=Basilar occlusions to 12 hours
The 2015 Endovascular Revolution
• Five major positive trials of endovascular therapy all published in 2015 in NEJM
• Trial design somewhat differed, but common to each:
  – 1. Used newer-generation devices
  – 2. Selected patients who were eligible via CTA (less commonly perfusion)
  – 3. IV t-PA in those who were eligible followed by embolectomy
  – 4. At least 6 hour time window

What do we do given this data?
• 1. All patients eligible for IV t-PA should receive it (quickly)
• 2. Patients within 6* hours (for now) should receive a CTA to look for a large vessel occlusion (LVO)
• 3. If LVO present, endovascular therapy should occur, even following IV t-PA
• Fundamental shift in hospital protocols including transfer protocols

What’s coming: 2017-2018
• DAWN and DEFUSE3 Trials
• Select patients with LVO treated up to 24 hours based on complex perfusion selection
  – Automated CT software
• Will lead to reexamination of triage and ED/hospital protocols once again

Case 2
• A 76 year-old man with a history of smoking presents with 3 days of R hand weakness
• Examination shows a R pronator drift and slowed movements of the R hand
• The patient takes aspirin 81mg daily as well as lisinopril
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  
• TEE superior to TTE for: LA appendage, R to L shunt, examination of aortic arch  
• Recent study: TEE found additional findings in 52% and changed management in 10%  


Atrial Fibrillation Detection

• EKG  
• 48 Hours of Telemetry  
• Long-term cardiac event monitor (>21d)  
  – 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 or Carotid dissection
4. Rare hypercoagulable states: APLS

The Mess of PFOs in Stroke

- Around 20% of all patients have PFO
- PFO alone not necessarily associated with higher risk of recurrent stroke
  - High risk: Large, associated atrial septal aneurysm
- Three previous negative trials of closure devices
  - Cardiologists still performing these procedures widely
- New data coming in 2017: select closures

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 70 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
- 2016: Not all pts benefit
  - CYP2C19 loss of function


**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
- We typically stop all meds except half-dose β-blockers

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 73 year-old woman 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 176/97

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
Differential for Transient Focal Neurologic Deficit

- The Big Three
  - 1. Stroke/TIA
  - 2. Seizure
  - 3. Complicated Migraine

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 vs. CEA: CREST Trial
- 4-year study of 1321 symptomatic and 1181 asymptomatic patients randomized to CEA vs. 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

Result confirmed over 5 years in a 2015 trial

Case 5

- A 54 year-old man with a history of HTN comes to your office concerned as his mother just died after an ischemic stroke. He wants to know what primary preventative interventions can reduce his chances of having a similar event.
Primary Prevention Guidelines

• Risk estimation schemes
• Treat vascular risk factors and encourage physical activity
• Anticoagulants for afib
  – CHA2DS2-VASc score
    • ≥2=anticoagulate
    • 1=consider anticoagulation

Asymptomatic Carotid Stenosis

• Some benefit for endarterectomy in asymptomatic stenosis
  – >60% or >80% cut-offs
  – Must have a very low perioperative risk of stroke and death to realize benefit (3%)
• Data much less convincing than symptomatic trials (CREST2 underway)
• Do not screen low risk patients (and probably shouldn’t screen anyone)

Antiplatelets to prevent stroke?

• Consider low-dose ASA in specific populations based on risk stratification schemes
  – 1. 10-year risk > 10%
  – 2. Women (esp with DM)
  – 3. Chronic kidney disease (but not stage 4 or 5)
• In all cases, since data marginal, balance risk of hemorrhage

Meschia J et al. Stroke, 2014