

# 2019 Update in Diagnosis and Management of Stroke

---



**S. Andrew Josephson MD**

Carmen Castro Franceschi and Gladys K. Mitchell Neurohospitalist Distinguished Professor  
Chair, Department of Neurology  
Founder, Neurohospitalist Program  
University of California, San Francisco

*The speaker has no disclosures*

# Case 1

- A 65 year-old right handed man with a history of HTN presented to the ED in a delayed fashion after the sudden onset of right sided weakness.
- Exam shows an expressive aphasia, R face and arm weakness as well as R visual field cut and L gaze deviation
- He was last seen normal at 1 p.m., and it is now 8:45 pm

# UCSF “Stroke Protocol” CT

- Obtained at UCSF in suspected acute stroke and TIA patients hours from onset
  1. Non-contrast CT of the head
  2. CT Angiography from aortic arch to the top of the head
  3. CT Perfusion study
  4. Post-contrast CT of the head

What treatment should this patient likely receive?

- A. IV t-PA alone
- B. IV t-PA followed by embolectomy
- C. Embolectomy alone
- D. IV heparin
- E. Antiplatelets

# The 2019 Acute Stroke Timeline

- Time of onset= last time seen normal

0-4.5 Hours

IV-tPA

0-6 Hours

Mechanical

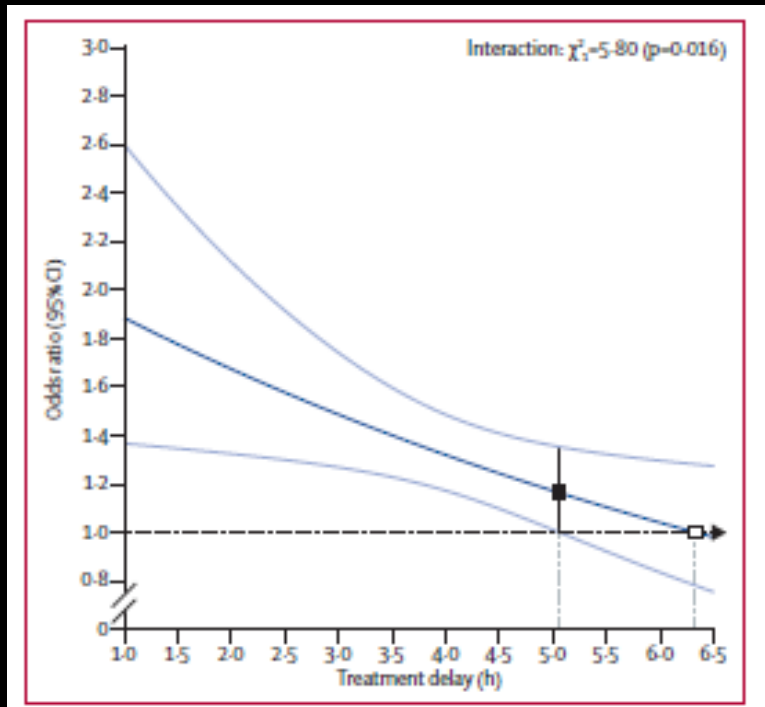
Embolectomy for all

6-24 Hours

Mechanical

Embolectomy for some

# Intravenous t-PA: Broad Success



	Alteplase (n=3391)	Control (n=3365)		Odds ratio (95% CI)*
<b>Treatment delay</b>				
<3.0 h	259/787 (32.9%)	176/762 (23.1%)		1.75 (1.35-2.27)
>3.0-4.5 h	485/1375 (35.3%)	432/1437 (30.1%)		1.26 (1.05-1.51)
>4.5 h	401/1229 (32.6%)	357/1166 (30.6%)		1.15 (0.95-1.40)
<b>Age (years)</b>				
<80	990/2512 (39.4%)	853/2515 (33.9%)		1.25 (1.10-1.42)
>80	155/879 (17.6%)	112/850 (13.2%)		1.56 (1.17-2.08)
<b>Baseline NIHSS score</b>				
0-4	237/345 (68.7%)	189/321 (58.9%)		1.48 (1.07-2.06)
5-10	611/1281 (47.7%)	538/1252 (43.0%)		1.22 (1.04-1.44)
11-15	198/794 (24.9%)	175/808 (21.7%)		1.24 (0.98-1.58)
16-21	77/662 (11.6%)	55/671 (8.2%)		1.50 (1.03-2.17)
≥22	22/309 (7.1%)	8/313 (2.6%)		3.25 (1.42-7.47)

0.5 0.75 1 1.5 2 2.5  
Alteplase worse      Alteplase better

# 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

# 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
  - 3. IV t-PA in those who were eligible followed by embolectomy
  - 4. Typically a 6 hour time window



# The 2018 Second Revolution

- DAWN and DEFUSE3 Trials
- Select patients with LVO treated up to 24 hours based on CT perfusion selection
  - Automated CT software widely available
- Has led to major reexamination of triage and ED/hospital protocols

# What do we do given this data?

- 1. All patients eligible for IV t-PA should receive it (quickly)
- 2. Patients within 6 hours 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 regardless of perfusion data

# What do we do given this data?

- 4. If the patient has a LVO and presents between 6-24 hours, CT perfusion is required and selects patients who should receive endovascular therapy
- 5. Consider IV tPA for some outside of the 4.5 hour window with MRI selection

# Wait!

## What about tPA Out of the Window?

- A substantial number of patients wake up with a stroke or they can't tell us their time of onset
- Some will have had a stroke in the last few hours and therefore IV tPA may work
- Important positive trials used either MRI to select these patients (+DWI but -FLAIR) or CT/MR perfusion imaging
- Prime time?

Thomalla et al: *N Engl J Med* 379:611, 2018

Ma et al: *N Engl J Med* 380:1795, 2019

## Case 2

- A 65 year-old man with a history of HTN presents with 3 days of R arm weakness
- Examination shows a R pronator drift and mild weakness in the extensors of the R hand and arm
- The patient takes aspirin 81mg daily as well as HCTZ

Which of the following is not part of the standard embolic 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
- More recently: 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

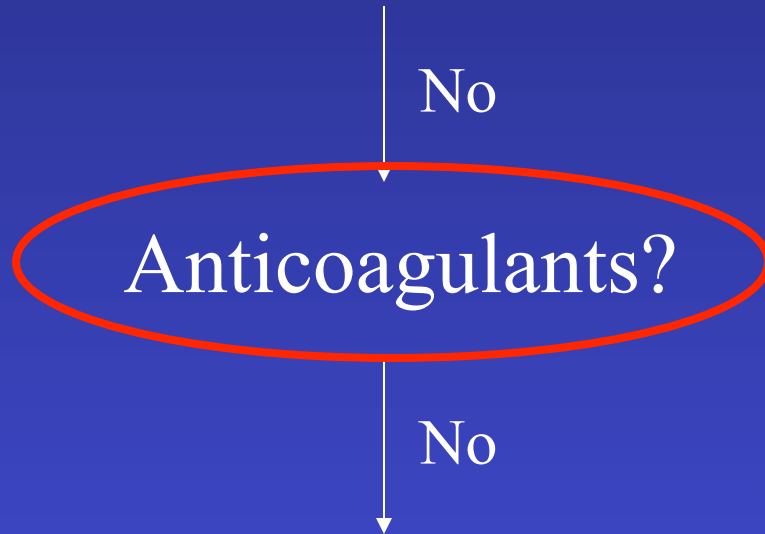
Acute Stroke Therapy?

No

Anticoagulants?

No

Antiplatelets



# Shrinking Indications for Anticoagulation in Stroke

1. Atrial Fibrillation
2. Some other cardioembolic sources
  - Thrombus seen in heart
  - ~~?EF < 35~~ WARCEF 2012
  - ~~?PFO with associated Atrial Septal Aneurysm~~
3. ~~Vertebral or Carotid dissection~~ CADISS 2015
4. Rare hypercoagulable states: APLS

# The “Absolute Mess” of PFO in Stroke

Meier B and Lock JE *Circulation*. 107:5, 2003

- Around 20-25% of all patients have a PFO
- PFO alone is not necessarily associated with higher risk of recurrent stroke
  - Higher risk: Larger PFO, associated atrial septal aneurysm, perhaps younger age
- Three previous *negative* trials of closure devices but cardiologists pre-2017 were still performing these procedures widely

# More Actionable Data

	RESPECT	Gore REDUCE	CLOSE
Inclusion Criteria	Cryptogenic stroke within past 270 days + PFO	Cryptogenic stroke within past 180 days + PFO	Stroke attributed to PFO + atrial septal aneurysm OR large PFO
Participants	980 participants	644 participants	663 participants
Intervention Arm	PFO closure	PFO closure + antiplatelet	PFO closure + antiplatelet
Medical Rx Arm	Antiplatelet or anticoagulation	Antiplatelet	Arm 1: antiplatelet Arm 2: anticoagulation
Results	Less recurrent stroke with PFO closure (NNT 42)	Less recurrent clinical and clinical+radiographic stroke with PFO closure (NNT 28)	Less recurrent stroke with PFO closure (NNT 20)

*N Engl J Med, 2017*

## What now?

“Let’s close all these PFOs!”

- DO NOT close all these PFOs
- DO screen patients for PFO (?how)
- It is sensible to discuss with your cardiologists some “Rules of the Road”
- At the end of the day, this is an exciting advance for some (young) people with stroke that can make a substantial impact on recurrence rates

# Rules of the Road

- Consider PFO closure if:
  - The patient is younger than 60 years old
  - AND you can be sure the PFO is the most likely etiology after a thorough workup
  - AND the qualifying event is a stroke (not TIA) that appears embolic (not lacunar)
  - Likely concentrate on large PFOs or those with an atrial septal defect
    - Cardiologists new task: start counting bubbles

# Risks to Discuss With Your Patients

- Atrial Fibrillation rates higher
- No great data beyond 5-10 years
- Antiplatelet regimens variable but most include duals for some time and then monotherapy
  - And what if AF develops?
- Major risk for stroke is up front rather than spread throughout subsequent years
- Medical management: Options appear equal



# Heparin in Acute Stroke

- Study examined the 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

## Case 3

- A 70 year-old woman with a history of DM, smoking presents 10 hours after the onset of slurred speech and right arm and leg weakness.
- The patient is taking 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?



Anticoagulants?



Antiplatelets

# Antiplatelet Options

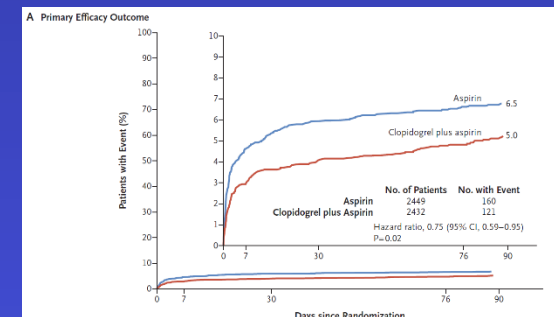
- 1. ASA
  - 50mg to 1.5g equal efficacy long-term
- 2. Aggrenox
  - 25mg ASA/200mg ER Dipyridamole
- 3. Clopidogrel (Plavix)
  - Multiple secondary prevention studies (CHARISMA, SPS3) show no long-term benefit in combination with ASA

# 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?

- POINT trial
- Select those with only minor or no deficits (NIHSS 3 or less or ABCD2 of 4 or more)
- Nearly 5000 TIA or Minor Stroke patients assigned to 90d of daily ASA + Placebo versus daily ASA + Clopidogrel following 600mg load
- Modestly improved efficacy (1.5%)
- Minimally (0.5%) more hemorrhage



# When to use Dual Antiplatelets

- NOT all the time!
- After minor stroke or TIA for only 21\* days
- After a fresh carotid or coronary stent
- With severe intracranial atherosclerosis (>70%) and stroke/TIA in that territory for only 90 days



# Other Acute Stroke Management

- Statins for (almost) all patients with stroke or TIA
  - 80mg atorvastatin if LDL>100 for at least 5 years
- Tight Glucose and Fever control in acute period
- Enoxaparin for DVT prophylaxis (better than compression stockings or UFH)

# 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  $\beta$ -blockers and (maybe) clonidine

# 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

# 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: ABCD<sup>2</sup> 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

Johnston SC et al: *Lancet* 369:283, 2007

# 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 ABCD<sup>2</sup> prediction
- 2. EXPRESS study
  - 80 percent reduction in risk with urgent TIA clinic visit versus usual primary care visit in 1278 patients



# TIA Aggressive Therapy: A Modern Look

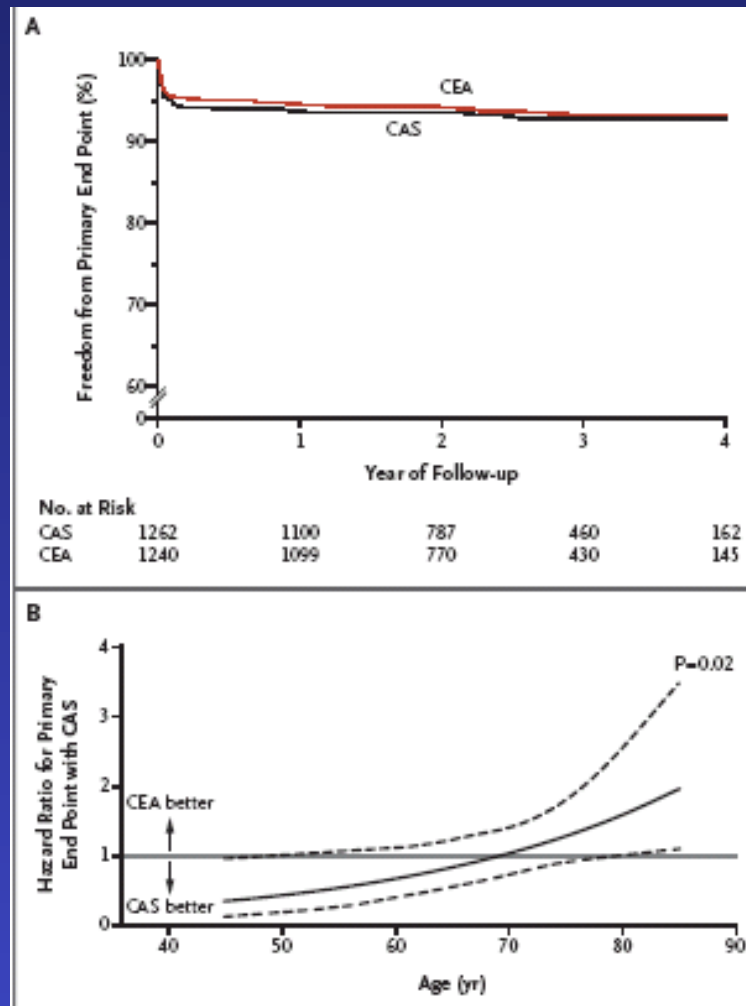
- 2009-2011 TIA registry of nearly 5000 patients
- Population at baseline was high risk as with historical cohorts
- 78% saw a stroke specialist within 24 hours
  - Hospitalists not mentioned in this European study
- 1-year stroke rate was 5.1%
- Rates at 2d, 7d, 30d, 90d, 1y were all less than half of that in historical cohorts

# 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

Brott TG et al: *N Engl J Med* 2010  
 Bonati LH et al: *Lancet* 2015