Inpatient Management & Secondary Risk Reduction of Stroke & TIA

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Disclosures

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Has no relationships with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on patients.
Objectives

1. Review recommendations re: tx of elevated BP
2. Review evidence for anti-platelet tx
3. Review role of statins in stroke/TIA
4. Discuss evidence surrounding correction of carotid artery stenosis
5. Review indications for anticoagulation
Immediate Management Goals

1. Ensure medical stability.
2. Quickly reverse any conditions that are contributing to the patient’s problem.
3. Screen for potential contraindications to thrombolysis in acute ischemic stroke patients.
4. Move toward uncovering the pathophysiologic basis to the patient’s neurologic symptoms.
5. Reduce risk for recurrent stroke.
Initial Treatments

- HOB
- Hyperglycemia
- Fever
- Blood Pressure
Initial Treatments

• HOB
  – Cerebral perfusion pressure is maximal when HOB @ 0°
  – Mean flow velocity decreases by 20% w/ HOB @ 30°
  – Recommend HOB be as flat as possible during the 1st 24 hrs (0-15°) unless contraindicated
  – Not recommended in pts with intracerebral hemorrhage

• Hyperglycemia
• Fever
• Blood Pressure
Initial Treatments

• HOB

• Hyperglycemia
  – Independently associated with poor functional outcome
  – Hyperglycemia worsens ischemic damage in animal models
  – Glucose reduction reduces ischemic damage in experimental models
  – Acute hyperglycemia is associated with reduced salvage of penumbral tissue and greater final infarct size by neuro-imaging
  – Hyperglycemia is associated with reduced benefit from recanalization with thrombolytic therapy and higher odds for symptomatic intracerebral hemorrhage
  – Recommendation is to tx BS > 140 to 180

• Fever

• Blood Pressure
Initial Treatments

• HOB
• Hyperglycemia
• Fever
  – Investigate etiology (e.g., meningitis, subdural empyema, brain abscess, IE)
  – Fever may contribute to brain injury in pts with acute stroke
  – Body temperature is independently related to the initial stroke severity and infarct size
  – For each 1° increase, relative risk of poor outcome rises by 2.2%
  – Treat with Tylenol
• Blood Pressure
Initial Treatments

- HOB
- Hyperglycemia
- Fever
- Blood Pressure
  - Hypertension is the #1 risk factor for stroke
  - Our approach to elevated BP can be neuro-protective or injurious
A 74-year-old woman is admitted to the hospital after sustaining a severe left hemispheric ischemic stroke while alone at home. The patient has hypertension for which she takes enalapril.

On exam, BP is 190/105, pulse is 80. She has right hemiparesis, right facial droop, aphasia, and dysarthria. The remainder of the exam is normal. Labs are normal.

A CT scan shows frank ischemic changes that occupy most of the left middle cerebral artery territory. An ECG and CXR are normal.
Question 1

Which of the following is the most appropriate treatment of her hypertension at this time?

A. Intravenous labetalol
B. Intravenous nicardipine
C. Oral nifedipine
D. Withholding of all antihypertensive medications
An 80-year-old man is brought to the ED within 45 minutes of the witnessed onset of dysarthria and right face, arm, and leg weakness. rtPA is administered intravenously 105 minutes after symptom onset. The patient is then admitted to the ICU, and 4 hours after thrombolysis, his neurologic symptoms and signs are rapidly improving. BP is 190/105. There is right pronator drift, right facial droop, and mild residual dysarthria.
Question 2

Which of the following is the most appropriate treatment of this patient’s elevated blood pressure?

A. Intravenous labetalol
B. Intravenous nitroprusside
C. Oral nifedipine
D. Withholding of antihypertensive medications
Hypertension

• Autoregulation disrupted in ischemic stroke

• Ambulatory setting:
  – Goal: SBP ≤ 140 (or ≤ 130 if diabetic)

• Uncomplicated ischemic strokes (no dissection or CHF)
  – Elevated BP tolerated as long as SBP is < 220 or the DBP is < 120
  – Restart BP meds after 24 hours (IIa C)

• Ischemic strokes treated with lytics:
  – SBP < 180, DBP < 105 x 24 hours after rtPA treatment

• Euvolemia
  – Isotonic fluids
Hypertension

- Labetalol 10 mg IV over 1-2 min, may repeat every 10–20 min, max dose of 300 mg
- Labetalol 10 mg IV followed by infusion at 2–8 mg/min
- Enalapril test dose 0.625 mg, then 1.25–5 mg IV push Q 6h
- Nicardipine infusion 5mg/h, titrate up to desired effect by increasing 2.5 mg/h every 5 min to max of 15mg/h
- If BP not controlled, consider nitroprusside 0.1-10 mcg/kg/min
- Do not lower BP by more than 15% in the first 24 hrs.
Hypertension

Penumbra

- In pts w/ ischemic stroke, the perfusion pressure distal to the obstructed vessel is low and the distal vessels are dilated.
- Blood flow through these vessels is dependent upon systemic BP
- Body’s protective response is to acutely raise systemic BP
- Observed that BP falls by 20/10 within 10 d following acute ischemic stroke
Anti-platelet Therapy
ASA vs. Coumadin

Warfarin ASA Recurrent Stroke Study (WARSS)

- 2,206 pts at 47 US centers; double-blind study
- Stroke/TIA pts: **ASA 325 vs. Warfarin INR 1.4 - 2.8**
- Primary Outcome: Recurrent ischemic stroke or death
- Secondary Outcome: TIAs, MI, Hemorrhage
- The rates of major hemorrhage were low (2.22 per 100 patient-years in the warfarin group and 1.49 per 100 patient-years in the aspirin group).
- There were **no statistical differences in primary or secondary endpoints** – e.g. coumadin is no better than ASA for cryptogenic stroke.

MATCH Trial

- 7,599 pts recent TIA/Stroke & 1 risk factor (28 countries)
- Clopidogrel + ASA 75 vs. Clopidogrel + Placebo
- **No Significant Difference in Endpoints:** MI, ischemic stroke, vascular death.
- **Increase** in life-threatening bleeding (2x higher) and major bleeding in pts on both drugs (3% vs. 1%, & ICH more common).

*Summary of MATCH Results*

*Adapted from reference 4*

*Lancet 2004; 364: 331-337*
Clopidogrel + ASA

SPS3 Trial

- 3,020 pts, small subcortical infarct within 6 months
- Clopidogrel + ASA 324 vs. ASA 324
- Stopped early (2011)

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<th>Bleeding Risk</th>
<th>CNS Bleeding</th>
<th>All Cause Mortality</th>
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<tbody>
<tr>
<td>Dual Tx</td>
<td>6.5%</td>
<td>5.5%</td>
<td>5.8%</td>
</tr>
<tr>
<td>ASA</td>
<td>3.3%</td>
<td>2.5%</td>
<td>4.1%</td>
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</table>

Intl. Stroke Conference 2012 (New Orleans)
Clopidogrel vs ASA + ERDP

PROFESS Trial
- Largest 2º stroke prevention trial ever (2003-2008)
- 20,332 Pts, 695 Sites, 35 countries
- Plavix vs. ASA + ER dipyridamole
- Primary outcome: Recurrent stroke
- Secondary: Stroke, MI, or Vasc Death
- Could NOT prove Non-Inferiority of ASA + ERDP

[Data chart showing comparisons between Aspirin-ERDP and Clopidogrel]

*NEJM*, Sept 18, 2008; 359 (12):1238-1251
SPARCL trial

- 4,731 patients with recent stroke (LDL-c 100 – 190) randomized to atorvastatin 80 mg daily or placebo.
- Mean follow-up: 4.9 years
- Primary end point: Any non-fatal or fatal stroke
- Atorvastatin group: 11.2%
  - 218 ischemic, 55 hemorrhagic
- Placebo group: 13.1%
  - 274 ischemic, 33 hemorrhagic
- 5-yr absolute risk reduction for stroke: 2.2%
- **NNT = 45**
- 5-yr absolute risk reduction for major CV events: 3.5%
Inpatient statin use predicts improved ischemic stroke discharge disposition

Observational study: analyzed discharge disposition among 12,689 patients with ischemic stroke from 2000 – 2007 at 17 hospitals.

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<th>Home</th>
<th>Death</th>
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<tbody>
<tr>
<td>No prior statin use</td>
<td>50.0%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Prior statin use</td>
<td>54.6%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Prior statin use &amp; continued</td>
<td>56.5%</td>
<td>5.5%</td>
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<tr>
<td>Prior statin use but D/C’d</td>
<td>39.1%</td>
<td>22.3%</td>
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Large Vessel Workup

- **Cardioembolic:**
  - Afib, intracardiac thrombus, paradoxical embolus
  - Telemetry
  - TEE

- **Aortic Arch**
  - TEE

- **Carotids**
  - Carotid imaging (US, CTA, MRA)

- **Intracranial Vessels**
  - Intracranial imaging (CTA, MRA)

- **Patent Foramen ovale**
Intracranial Arterial Stenosis

**SAMMPRIS Trial**
- Pts with intracranial artery stenosis (70-99%)
- Randomized to medical arm vs. angioplasty & stenting
- **Medical arm:**
  - Dual antiplatelet tx (ASA + Plavix)
  - SBP ≤ 140
  - LDL-c ≤ 70
  - HbA1c ≤ 7.0%
  - Lifestyle Modifications (smoking cessation/weight loss)
- **30-day rate of stroke or death:**
  - Angioplasty & stenting group: 14.7%
  - Medical group: 5.8%
  - Outcomes equal 30-365 days.
Closure vs. medical therapy in cryptogenic stroke

- **CLOSURE I Study**
- 909 pts 18-60 with cryptogenic stroke/TIA and PFO
- Closure vs ASA vs Warfarin
- No deaths w/in 30 days
- Incidence of death w/in 2 years
  - PFO closure group: 5.5%
  - Medical therapy group: 6.8%
- No deaths from neurologic causes within 2 years.
- Closure does not offer a greater benefit than medical therapy alone for secondary stroke prevention.
- Closure led to more A-fib conversion (5.7% vs 0.7%)

Carotid Artery Stenosis

How to manage carotid artery stenosis?

Carotid Endarterectomy (CEA) Vs. Carotid Stenting
How to manage carotid artery stenosis?

- **NASCET** in early 1990’s
  - Comparison: CEA vs. best medical management at the time.
  - Benefit: CEA for pts with symptoms ipsilateral to 70-99% stenosis
  - Limited Benefit: 50-69% symptomatic stenosis, especially in women.

- **SPACE Trial** (*Lancet* 10/2006)
  - 1,200 pts with recent CVA/TIA randomized to CEA vs. stenting

- **EVA-3S** (*NEJM* 10/2006)
  - 527 pts with recent CVA/TIA randomized to CEA vs. stenting

- Both failed to demonstrate non-inferiority
  - In EVA-3S, stenting associated with significantly more short-term stroke and death.
Carotid Artery Stenosis

How to manage carotid artery stenosis?

• SAPPHIRE (NEJM 10/04 and 4/08)
  – For high risk patients, stenting is as good as CEA

• CREST Trial (NEJM 7/10)
  – 4 year study of 1,321 symptomatic and 1,181 asymptomatic pts randomized to CEA or carotid stenting
  – Combined endpoint of stroke, MI, death not significantly different
  – More strokes in 1st 90 days in stenting group
  – More MI’s in surgical group
  – Similar endpoints after 90 days.
Carotid Artery Stenosis

When to fix the carotid artery?

The Bottom Line...

- Patients with symptomatic carotid stenosis 70-99% should be revascularized.
  - If non-disabling stroke or TIA, within 2-6 weeks.
- If > 70 yrs old, CEA preferred unless high risk surgical candidate.
- If < 70 yrs old, must weigh risks of perioperative MI vs. stroke.
CEA should **not** be performed in pts with:

- Medical conditions that greatly increase surgical risk
- Radiation-induced stenosis
- Restenosis after CEA
- Carotid dissection
- History of radical neck surgery
- Unfavorable anatomy
  - Stenosis above the C2 level
  - Ostial lesion below the clavicle
  - Spinal immobility
  - Presence of a tracheostomy stoma
  - Contralateral laryngeal nerve paralysis
Cryptogenic Stroke

- 30% of strokes are cryptogenic
- Most common unrecognized cause = PAF (25%)
- Second most common cause = Aorta atheroma
Detecting Afib

- ECG
- 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

The Bottom Line...

- Extended cardiac telemetry should be a part of the standard workup if no other source is detected and if the patient could be anticoagulated if Afib were to be found.

Kamel, H. et al: *Stroke* 41:1514, 2010
Atrial Fibrillation

CHADS\textsubscript{2} Score

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<tr>
<td>H HTN</td>
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<tr>
<td>A Age $\geq$ 75</td>
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<td>D Diabetes</td>
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Annual Stroke Risk

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<td>5</td>
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Coumadin vs ASA

Warfarin vs ASA in Reduced Cardiac EF (WARCEF)

- 2,305 pts, EF < 35 % (sinus rhythm)
- INR 2.5 avg vs. ASA 325
- No overall decreased risk of composite of death, ischemic stroke, ICH
- Fewer ischemic strokes with coumadin (29 vs. 55), more ICH (5 vs. 2), but absolute risk very low anyway

*NEJM*, May 17, 2012; 366; 1859-1869
Anticoagulation

• Atrial Fibrillation

• Some other cardioembolic sources
  – Intracardiac thrombus
  – ? LV EF < 35%
  – ? PFO with associated Atrial Septal Aneurysm

• Carotid or Vertebral dissection

• Rare hypercoagulable states (APS)
A 52-year-old woman is admitted after a TIA that has since resolved. She smokes 1.5 packs of cigarettes daily and wants help quitting. She has tried quitting on 3 previous occasions, each time using nicotine patches, and she would like to try something different. She has a seizure disorder that is well controlled on valproate.

In addition to brief smoking cessation counseling, which of the following is the most appropriate pharmacologic therapy to offer?

A. Bupropion
B. Nortriptyline
C. Sertraline
D. Varenicline
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In addition to brief smoking cessation counseling, which of the following is the most appropriate pharmacologic therapy to offer?

A. Bupropion
B. Nortriptyline
C. Sertraline
D. Varenicline
Summary

• Aggressive medical management
  – Anti-platelet therapy
  – SBP ≤ 140 (or ≤ 130 if diabetic)
  – LDL-c ≤ 70
  – HbA1c ≤ 7.0%
  – Smoking cessation
  – Weight loss
  – Dietary modifications

• Fix symptomatic ipsilateral carotid disease

• Anticoagulate when appropriate

• Do not chase PFOs or intracranial arterial stenoses