The Year in Neurology: Headlines Relevant to the Primary Care Provider

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Disclosures
none

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Outline

• Stroke
  – TIA
  – Carotid stenting
  – Permissive hypertension
  – New oral anticoagulants

• Multiple Sclerosis
  – Approaches to diagnosis and therapy
  – Oral medications

Case 1

• One of your patients calls your office because he experienced 2 hours of right arm weakness and trouble speaking earlier in the day. He measured his blood pressure at 150/85 just after the episode. He is a 63 year-old man with hypertension and diabetes, taking aspirin, lisinopril, and metformin.
Question 1: Which of the following is the most appropriate management strategy?

1. See the patient in your office that day and perform an EKG; order a routine head CT, carotid ultrasound and echocardiogram
2. Send the patient to the emergency room for urgent head and vascular imaging, an EKG and echocardiogram
3. Tell the patient he was lucky he didn’t have a stroke and advise him to take an extra aspirin
4. Order a routine carotid ultrasound, EKG and echocardiogram and schedule him for a visit with you in one week

TIA: Unstable Angina of the Brain

- 10% will have a stroke in 90 days
- Half of these will occur in the first 2 days

- Is there a way to identify who is at highest risk?
- Is there anything you can do to prevent stroke after TIA?

Johnston et al, Lancet 2007

TIA workup

Antiplatelets (aspirin, clopidogrel, Aggrenox, cilostazol*)
Carotid endarterectomy or stent

Anticoagulation

High Risk TIA: The ABCD² Score

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 60</td>
<td>1 point</td>
</tr>
<tr>
<td>Blood pressure ≥ 140/90</td>
<td>1 point</td>
</tr>
<tr>
<td>Clinical Symptoms</td>
<td></td>
</tr>
<tr>
<td>Speech impairment without weakness</td>
<td>1 point</td>
</tr>
<tr>
<td>Unilateral weakness</td>
<td>2 points</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 point</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
</tr>
<tr>
<td>10 to 59 minutes</td>
<td>1 point</td>
</tr>
<tr>
<td>≥ 60 minutes</td>
<td>2 points</td>
</tr>
</tbody>
</table>

Johnston et al, Lancet 2007
### TIA: EXPRESS Study

**Workup**
- Brain imaging
- EKG
- Carotid ultrasound
- Echocardiogram

**Treatment**
- 300 mg aspirin in clinic and daily for 4 weeks
- Clopidogrel in high risk patients (with 300 mg loading dose)
- Simvastatin 40 mg daily
- Perindopril if SBP > 130

### Outcomes: stroke within 90 days

<table>
<thead>
<tr>
<th></th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>p*</th>
</tr>
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<tbody>
<tr>
<td>Whole population</td>
<td>63/643</td>
<td>27/644</td>
<td>0.0001</td>
</tr>
<tr>
<td>Presented with TIA</td>
<td>29/333</td>
<td>11/252</td>
<td>0.0015</td>
</tr>
<tr>
<td>Presented with stroke</td>
<td>14/401</td>
<td>16/192</td>
<td>0.0077</td>
</tr>
<tr>
<td>Outpatient care</td>
<td>33/323</td>
<td>6/268</td>
<td>0.0001</td>
</tr>
<tr>
<td>Referred to clinic</td>
<td>32/310</td>
<td>6/281</td>
<td>0.0001</td>
</tr>
<tr>
<td>Presented with TIA</td>
<td>16/365</td>
<td>1/127</td>
<td>0.0001</td>
</tr>
<tr>
<td>Presented with stroke</td>
<td>17/358</td>
<td>5/325</td>
<td>0.037</td>
</tr>
<tr>
<td>Hospital-based care</td>
<td>23/285</td>
<td>19/222</td>
<td>0.23</td>
</tr>
<tr>
<td>Discharged from A&amp;E</td>
<td>5/33</td>
<td>5/36</td>
<td>0.42</td>
</tr>
<tr>
<td>Inpatient care</td>
<td>18/252</td>
<td>14/268</td>
<td>0.30</td>
</tr>
<tr>
<td>Presented with TIA</td>
<td>9/56</td>
<td>8/277</td>
<td>0.56</td>
</tr>
<tr>
<td>Presented with stroke</td>
<td>14/119</td>
<td>11/255</td>
<td>0.28</td>
</tr>
</tbody>
</table>

* p-values indicate statistical significance.
Case 1

- You send your patient to the emergency department. He is found to have a 90% left carotid stenosis.
- Should you refer him for carotid stenting or carotid endarterectomy?
CEA vs. Stenting

- CREST Trial: 2522 patients randomized to CEA vs. carotid stenting
  - TIA or stroke within the previous 6 months AND angiogram with > 50% stenosis or ultrasound with > 70% stenosis
  - Asymptomatic AND angiogram with > 60% stenosis or ultrasound with > 70% stenosis
- Four year follow up

Brott et al, NEJM 2010

CEA vs. Stenting

- Peri-procedural stroke
  - 4.1% in stenting group vs. 2.3% in CEA group; p=0.01
- Peri-procedural MI
  - 1.1% in stenting group vs. 2.3% in CEA group; p=0.03
- Combined endpoint of stroke, MI, or death within 30 days or ipsilateral stroke within 4 years: similar between groups

Brott et al, NEJM 2010

CEA vs. Stenting

- Meta-Analysis of three trials: EVA-3S, ICSS, and SPACE
- 3454 patients with stroke or TIA and >50% carotid stenosis
- Stroke or death within 120 days higher in stenting group (8.9% vs. 5.8%; p=0.0006)
- MI was rare in both groups (0.2% vs. 0.4%)

Bonati et al, Lancet 2010

Age modifies risk in CEA vs. stenting

Brott et al, NEJM 2010
More data on age in CEA vs. stenting

<table>
<thead>
<tr>
<th>CAS</th>
<th>CEA</th>
<th>Risk ratio (95% CI)</th>
<th>Interaction p value</th>
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</thead>
<tbody>
<tr>
<td>EVA-35</td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>10 (7.9%)</td>
<td>127</td>
<td>10 (7.9%)</td>
</tr>
<tr>
<td>≥40 years</td>
<td>17 (12.3%)</td>
<td>138</td>
<td>7 (4.5%)</td>
</tr>
<tr>
<td>SPACE</td>
<td>&lt;40 years</td>
<td>10 (5.5%)</td>
<td>187</td>
</tr>
<tr>
<td>≥40 years</td>
<td>35 (13.5%)</td>
<td>260</td>
<td>19 (7.4%)</td>
</tr>
<tr>
<td>ICS</td>
<td>&lt;40 years</td>
<td>21 (5.3%)</td>
<td>395</td>
</tr>
<tr>
<td>≥40 years</td>
<td>51 (12.2%)</td>
<td>458</td>
<td>25 (5.5%)</td>
</tr>
<tr>
<td>Pooled</td>
<td>&lt;40 years</td>
<td>50 (7.8%)</td>
<td>469</td>
</tr>
<tr>
<td>≥40 years</td>
<td>105 (12.2%)</td>
<td>705</td>
<td>55 (6.9%)</td>
</tr>
</tbody>
</table>

Bonati et al, Lancet 2010

What about asymptomatic carotid stenosis?

ACES: Asymptomatic Carotid Emboli Study

- 482 patients with 70% stenosis
- 26 centers internationally
- Two 1-hour TCD recordings of ipsilateral MCA
- Followed for 2 years
- Outcome stroke or TIA

Halliday et al, Lancet 2010
ACES: Results

- 77 patients had embolic signals
- Annual risk of stroke
  - 0.70% if embolic signals absent
  - 3.62% if embolic signals present

Case 2

- You are covering the hospital and are called by the ED to admit an 83 year-old man who was brought in by ambulance after his wife found him with the inability to speak and right arm weakness. He has hypertension and diabetes and takes aspirin, metoprolol, hydrochlorothiazide, and glyburide at home.
- The last time his wife spoke with him was when he went to bed the night before.

CT Scan

Case 2

- You find the patient awake but with a global aphasia, a left gaze preference, a right facial droop and severe right arm weakness. His blood pressure is 210/105, heart rate 92, and his other vital signs are stable.
Question 2: What is the optimal management strategy for his blood pressure?

1. Lower to less than 185/95 with IV labetalol
2. Lower to less than 185/95 with nitropaste
3. Hold all of his blood pressure medications except the beta blocker and only treat him if his blood pressure exceeds 220/110
4. Do nothing acutely but continue his home blood pressure medications

Permissive Hypertension: COSSACS

Permissive Hypertension: SCAST

- Candesartan vs. Placebo: 2029 patients within 30 hours of stroke with SBP > 140

OR 1.17 (95% CI 1.00 – 1.38; p = 0.048)

Case 2

- You elect not to treat the patient’s blood pressure of 210/105. You start the patient on aspirin and a statin and admit him to the hospital.
Case 2

- Next day the patient’s telemetry strip reveals atrial fibrillation.

Afib: Aspirin plus Clopidogrel

**ACTIVE W**
- Warfarin vs. Aspirin plus Clopidogrel in 6706 pts
- Risk for primary outcome higher in aspirin/clopidogrel group (5.60% vs. 3.93%)
- Relative risk for stroke 1.44; p=0.0003
- Risk of major bleeding similar (2.42% vs. 2.21%)

**ACTIVE A**
- Aspirin vs. Aspirin plus Clopidogrel in 7554 pts
- Risk for stroke lower in aspirin/clopidogrel group (2.4% vs. 3.3%)
- Relative risk 0.72; p<0.001
- Risk of major bleeding higher with combination therapy (2.0% vs. 1.3%)
- Current guidelines recommend against combo

Question 3: Which of the following is **NOT** an evidence-based option for secondary stroke prevention in a patient with atrial fibrillation?

1. Aspirin
2. Clopidogrel
3. Aspirin plus Clopidogrel
4. Warfarin
5. Dabigatran
6. Apixaban

**RELY: Dabigatran vs. Warfarin**

- MI: RR 1.38 (95% CI 1.00 to 1.91) with dabigatran 150mg
- Bleeding rates similar
**AVERROES: Apixaban vs. Aspirin**

- **Stroke or Systemic Embolism**
  - **Apixaban**
    - Hazard ratio with apixaban: 0.45 (95% CI: 0.32–0.62)
    - 1.6% per year
  - **Aspirin**
    - 3.7% per year

**Bleeding and MI rates similar between groups**

**Summary: Stroke and TIA**

- Emergent workup and management of TIA reduces the rate of subsequent stroke
- CEA and carotid stenting may be equivalent in young patients, but stenting is probably harmful in patients >70 years old
- TCD may improve patient selection for CEA in asymptomatic carotid stenosis
- In acute stroke, permissive hypertension is probably not harmful but treating hypertension may be harmful
- Direct thrombin inhibitors are here and new factor Xa inhibitors are on the horizon

**Case 3**

- A 25 year-old woman with no past medical history presents with numbness and clumsiness in the right arm and leg for the last week. The symptoms progressed over 24 hours and have since stabilized. On examination, her right side has a mild pronator drift, slow finger and foot taps, and decreased vibratory sense in the hand and foot.

**MRI**
Multiple Sclerosis: Diagnostic Criteria

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS Diagnosis*</th>
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</thead>
<tbody>
<tr>
<td>2 or more clinical attacks</td>
<td>none</td>
</tr>
<tr>
<td>2 or more objective lesions</td>
<td></td>
</tr>
<tr>
<td>2 or more clinical attacks</td>
<td>Dissemination in space by MRI</td>
</tr>
<tr>
<td>1 objective lesion</td>
<td>Additional clinical attack</td>
</tr>
<tr>
<td>1 clinical attack</td>
<td>Dissemination in time by MRI</td>
</tr>
<tr>
<td>1 objective lesion</td>
<td>New lesions on later MRI</td>
</tr>
<tr>
<td>Insidious progression from</td>
<td>1 year of progression</td>
</tr>
<tr>
<td>onset</td>
<td>Dissemination in space by MRI</td>
</tr>
</tbody>
</table>

*No alternative diagnosis more likely

Polman et al, Ann Neurol 2011

Multiple Sclerosis: Workup

- MRI is the cornerstone of diagnosis
- Lumbar puncture is helpful but not always necessary if MRI is typical
- Labs: RPR/FTA-abs, ANA, SSA/SSB, B12
- Consider: HIV, Lyme, antiphospholipid antibodies, RF, aquaporin-4 antibodies, chest X-ray

MS: Natural History

- Clinically Isolated Syndrome
  - ≥ 3 brain lesions on MRI: 70-80% will progress to MS in 10 years
  - Normal brain MRI: <20% risk of developing MS

Clinically Isolated Syndrome:

- Probability of developing MS

![Graph showing probability of developing MS with different treatments and time periods.](attachment:graph.png)

Case 4

• A 35 year-old man with multiple sclerosis presents to your office with bilateral leg weakness. He has had similar symptoms with a relapse in the past and is requesting a course of steroids.

Question 5: The most appropriate next step would be:

1. Prescribe a one-week course of oral steroids
2. Give three days of high dose IV steroids
3. Perform a thorough review of systems and check a urinalysis

MS: pearls for the primary care provider

• Treatment of exacerbations with steroids only speeds the pace of recovery but does not enhance the ultimate degree of recovery
• Pseudo-exacerbations are a recapitulation of the symptoms of a prior attack
• Pseudo-exacerbations can be caused by heat, stress, systemic illness or infection
• Pseudo-exacerbations should not be treated with steroids

MS: Natural History

• Relapsing-remitting MS
  – On average, one attack every 9 months
  – After 15 years, 80% have functional limitation and 30-50% have SPMS and require assistance walking
  – After 25 years, 80% will require assistance walking
Relapsing Remitting MS: annual relapse rate

- Interferon Beta-1b
- Interferon Beta-1a
- Glatiramer
- Natalizumab


Oral drugs in RRMS: annual relapse rate

- Fingolimod vs Placebo
- Fingolimod vs Interferon
- Cladribine vs Placebo

Kappos et al, NEJM 2010; Cohen et al, NEJM 2010; Giovannoni et al, NEJM 2010

Adverse Events

- Glatiramer – injection site reactions
- Interferons – flu-like symptoms, depression
- Natalizumab – PML
- Fingolimod – bradycardia, zoster
- Cladribine – lymphopenia, zoster
- Rituximab – PML
- Alemtuzumab – pancytopenia, ITP, Graves’ disease, lymphoproliferative disorders

Thank you for listening

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Delays in assessment

<table>
<thead>
<tr>
<th>First call for medical attention</th>
<th>Phase 1 (n=310)</th>
<th>Phase 2 (n=283)</th>
<th>p</th>
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<tbody>
<tr>
<td>≤12 h</td>
<td>128 (41.3%)</td>
<td>105 (37.5%)</td>
<td>0.35</td>
</tr>
<tr>
<td>≤24 h</td>
<td>184 (59.4%)</td>
<td>160 (57.1%)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First call for attention to assessment in study clinic</th>
<th>≤6 h</th>
<th>≤24 h</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>5 (1.7%)</td>
<td>70 (23.4%)</td>
</tr>
<tr>
<td></td>
<td>80 (29.0%)</td>
<td>163 (59.1%)</td>
</tr>
</tbody>
</table>

SOS-TIA Study

- 24/7 TIA clinic in Paris, France
- 1089 patients evaluated; 1052 patients completed follow-up
- Workup: brain imaging, EKG, echocardiogram, and carotid ultrasound
- Treatment: aspirin, lipid and blood pressure lowering medications
- 90 risk of stroke: 1.24% (compared with 5.96% predicted rate based on ABCD² score)

ACES: Results

- Annual risk of stroke or TIA
  - 3.09% if embolic signals absent
  - 7.40% if embolic signals present

Acute (non-thrombolytic) Treatment

Aspirin

- IST: 19,435 pts
  - 2 week follow-up
    - Mortality 9.4 -> 9.0% (NS; NNT = 250)
    - Recurrent stroke 3.9 -> 2.8% (p < 0.001; NNT = 91)
- CAST: 21,106 pts
  - 4 week follow-up
    - Mortality 3.9 -> 3.3% (p = 0.04; NNT = 167)
    - Recurrent stroke 2.1% -> 1.6% (p = 0.01; NNT = 200)

Statin

- SPARCL: 4731 pts
  - 5 year follow-up
    - Recurrent stroke 13.1 -> 11.2% (p = 0.05; NNT = 53)
Atrial Fibrillation

**Warfarin**
- Pooled results from 5 placebo-controlled trials
- Relative risk reduction: 68%
- Annual stroke rate reduced from 4.5% → 1.4%
- NNT = 32
- Annual bleeding rate = 1.3% (versus 1% with placebo or aspirin)

**Aspirin**
- Pooled results from 3 placebo-controlled trials
- Relative risk reduction: 21%

Furie et al, Stroke 2011