Secondary Prevention in Stroke and TIA

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Stroke Facts

• 15 million/yr worldwide strokes
  - 5 million die
  - 5 million permanently disabled

• Risk factors
  1. High blood pressure and tobacco use
  2. Atrial fibrillation, heart failure and heart attack

• Incidence decreasing in developing countries, but absolute numbers continue to increase
  - Better BP treatment, less smoking
  - Aging populations

Deaths from stroke


Outline

- TIA
- Secondary Prevention
  - Lifestyle
  - Hypertension
  - Cardiac Risk Factors, Atrial Fibrillation
  - Ipsilateral Carotid Disease
  - Hyperlipidemia
  - Antithrombotic medications

Case

70 y/o patient with hypertension and diabetes presents to you for evaluation in the ER after a 30 minute episode of right sided weakness and aphasia. BP on initial evaluation was 158/94.

What is their risk of stroke in the next 2, 7, 30, 90 days?

TIA Statistics

AHA Heart Disease and Stroke Statistics 2008 Update
Circulation 2008;117:e25–e146

- ~15% of all strokes are heralded by a TIA
- 1/3 of classic definition TIs would be considered infarctions on the basis of diffusion-weighted magnetic resonance imaging findings
- Up to 300,000 per year in US
- Males and blacks have higher rates of TIA
- Approximately half of all patients who experience a TIA fail to report it to their healthcare providers
- After TIA, the risk of clinical events is high
### TIA – Short Term Stroke Risk

**JAMA 2000;284:2901-2906**

- 1707 TIA patients
- Stroke event rates:
  - 5.3% at 2 days
  - 10.5% at 90 days

### ABCD² or TIA Risk Stratification

<table>
<thead>
<tr>
<th>Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 60</td>
<td>1</td>
</tr>
<tr>
<td>BP &gt; 140/90 on first assessment after TIA</td>
<td>1</td>
</tr>
<tr>
<td>Clinical features</td>
<td>2</td>
</tr>
<tr>
<td>Unilateral weakness</td>
<td>1</td>
</tr>
<tr>
<td>Speech impairment without weakness</td>
<td>1</td>
</tr>
<tr>
<td>Duration of TIA</td>
<td>2</td>
</tr>
<tr>
<td>≥60 minutes</td>
<td>1</td>
</tr>
<tr>
<td>10–59 minutes</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
</tbody>
</table>

*Lancet 2007; 369: 283–92*
Risk of Stroke after TIA, Meta-analysis
Lancet Neurol 2007; 6:1063–72

<table>
<thead>
<tr>
<th>2 Day Risk</th>
<th>7 Day Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population based, face to face follow-up</td>
<td></td>
</tr>
<tr>
<td>Specialist Stroke Service (also earlier evaluations)</td>
<td></td>
</tr>
<tr>
<td>• Lower rates suggest early evaluation and treatments as effective approach</td>
<td></td>
</tr>
</tbody>
</table>

TIA - Short Term Risk Implications

• Need for prompt workup
  – At time of presentation
    • Especially if recent TIA or high ABCD² score?
  – In UW system, offer admission to most
• Testing/Interventions
  – Brain imaging (CT or MRI)
  – Carotid imaging
  – Cardiac imaging
  – Rx: antithrombotics, CEA, risk factors

Case

A 75 year old patient presents with left hemiparesis, about 12 hours after the onset of symptoms.

How can we help this patient avoid another stroke?
Secondary Ischemic Stroke Prevention
Factors to Consider

- Exercise, eat right, stop smoking
- Hypertension
- Atrial Fibrillation
- Carotid Stenosis/Occlusion
- Hyperlipidemia
- Antithrombotic Rx (Antiplatelet, Warfarin)
- Estrogen (HRT), Vitamins
- Special Conditions

### PROGRESS - Stroke Subtype

(Combined Results - Single + Combination)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of events/Total participants</th>
<th>Percent stroke reduction (PSPC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke</td>
<td>366/3551</td>
<td>34% (95 to 70%)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>314/3551</td>
<td>34% (95 to 70%)</td>
</tr>
<tr>
<td>Ischemia</td>
<td>314/3551</td>
<td>34% (95 to 70%)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>51/3551</td>
<td>80% (50 to 89%)</td>
</tr>
<tr>
<td>Hemorrhagic - intracerebrum</td>
<td>37/3551</td>
<td>80% (50 to 89%)</td>
</tr>
<tr>
<td>Stroke of Unknown Type</td>
<td>40/3551</td>
<td>40% (40 to 43%)</td>
</tr>
<tr>
<td>OVERALL</td>
<td>366/3551</td>
<td>34% (17 to 38%)</td>
</tr>
</tbody>
</table>

Stroke, 2004:35-116


Hypertension, Oct 2010
Cardiac Risk Factors

- Atrial Fibrillation
  - Prophylactic: Warfarin x 2m, then aspirin
- Mechanical heart valves: indefinite warfarin, add aspirin
- Bioprosthetic valves: 3 months, then aspirin

- Myocardial Infarction
  - Chest 2008;133;593S–629S
  - Mechanical: indefinite warfarin, add aspirin
  - Bioprosthetic: warfarin x 3m, then aspirin

- Congestive Heart Failure
  - Circulation 2009;119(12):1616–24
  - No great evidence for anticoagulation, antiplatelet

- Valvular Disease
  - LVH (~HTN), Patent foramen ovale (PFO), Atrial septal aneurysm, Spontaneous echo contrast, Valvular strands, Mitral annular calcification

Atrial Fibrillation
(usually Non-valvular Afib)

- Present in 20% of all brain infarcts
- Relative risk ~5 (15-20 for rheumatic dz)
- 1/3 will have a CVA, overall risk ~5%/yr
- Young and no risk factors, rate <=1%/yr
- History of stroke, rate ~12%/yr

TREATMENT
- Warfarin reduces risk 67%, ASA 20%
- LAA occlusion equivalent? Lancet 2009;374:534–42

Atrial Fibrillation with TIA/Stroke

Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY)

- Direct thrombin inhibitor, no monitoring
- 18,113 patients AF + risk factor, randomized to:
  - Warfarin
  - 110 mg/bid dabigatran
  - 150 mg/bid dabigatran
- Primary outcome: Stroke or systemic embolization

*Results were consistent in 20% with previous stroke/TIA


RE-LY Safety


Difference between NASCET and ECST in measurement of internal carotid artery stenosis

Approximate equivalent degrees of internal carotid artery stenosis used in NASCET and ECST according to recent direct comparisons

\[
A - B = \frac{A}{A}
\]

\[
\frac{46.03 - 11.32}{46.03} = \frac{34.71}{46.03}
\]

75.4% stenosis

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CEA for Symptomatic ICA Stenosis


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Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis

(International Carotid Stenting Study - ICSS)

- International RCT
- 1713 patients
- Recently symptomatic carotid disease
- interim safety analysis of 120-day stroke, death, or procedural MI
  - Longer term results still pending......
- Tried to ensure interventional experience
- 72% distal protection device

Lancet 2010; 375: 985–97
ICSS – Interim Main Results

<table>
<thead>
<tr>
<th>Event (primary or secondary endpoint)</th>
<th>N (Intervention Group)</th>
<th>N (Comparator Group)</th>
<th>N (% in Group)</th>
<th>N (% in Group)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke, death, or worsened neurologic deficit</td>
<td>75 (5.3%)</td>
<td>72 (5.2%)</td>
<td>282 (18.5%)</td>
<td>268 (17.0%)</td>
<td>0.348</td>
</tr>
<tr>
<td>Any stroke</td>
<td>20 (2.7%)</td>
<td>20 (2.7%)</td>
<td>80 (5.1%)</td>
<td>79 (5.0%)</td>
<td>0.787</td>
</tr>
<tr>
<td>Any death</td>
<td>15 (2.1%)</td>
<td>11 (1.6%)</td>
<td>60 (3.7%)</td>
<td>55 (3.4%)</td>
<td>0.261</td>
</tr>
<tr>
<td>Death due to stroke</td>
<td>14 (1.9%)</td>
<td>14 (2.1%)</td>
<td>56 (3.5%)</td>
<td>54 (3.3%)</td>
<td>0.540</td>
</tr>
</tbody>
</table>

Note: Data are number of deaths formed in the intervention group minus the number of deaths formed in the comparator group.

Table 3: Numbers are patients out of the total number of patients who were included in the study population.

ICSS - Conclusions

- CEA should remain the standard in most cases
- CAS can be considered

ICSS Substudy

- 231 patients
- MRIs before and after CEA/CAS
- New DWI lesions

References

Lancet 2010; 375: 985–97
Carotid Revascularization Endarterectomy vs. Stenting Trial

- NIH sponsored randomized trial
- 117 US and Canadian sites
- Interventionalists with demonstrated experience
- ~2500 patients, half asymptomatic
  - CEA: aspirin/alternative before+after
  - Stenting: aspirin/clopidogrel before+after
  - 96.3% distal embolic protection
- Primary Endpoints
  - Periprocedural stroke, MI, death AND
  - Ipsilateral stroke up to 4 years

CREST Main Results

CREST, Age Interaction
CREST – Conclusions

• Overall low event rates → better medical treatment
• More strokes with CAS, more MIs with CEA
• Similar findings in symptomatic vs. asymp.
• Overall equivalence suggests both safe and durable
• Editorial
  – Differing end point, but o/w c/w previous trials
  – MI has lesser impact on quality of life
  – CEA should still be considered standard of care for most, individualized decisions reasonable
  – Rx for asymptomatic patients controversial

Age modifies effect...

• EVA-3S, SPACE, ICSS individual patient meta-analysis

<table>
<thead>
<tr>
<th>Age</th>
<th>CAS</th>
<th>CEA</th>
<th>CAS vs. CEA (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>5/30</td>
<td>3/30</td>
<td>NS</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>10/70</td>
<td>8/70</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

Risk ratios of any stroke or death within 120 days of randomisation

Carotid Artery Occlusion

• Asymptomatic ⇒ benign prognosis
• Symptomatic
  – Incidence 6/100k/yr
  – 1/30 of ischemic strokes
  – Recurrence of stroke
    • 5.5%/yr all, 2.1% ipsi
    • 12.5%/yr all, 9.5% ipsi if impaired hemodynamics
    • 4.1%/yr all, 3.1% ipsi if severely impaired hemodynamics
• Management
  – Antiplatelet agents
  – If recurrent symptoms assess collateral/reserve
    • TCIs with CO2
    • SPECT w/Diamox
  – Consider
    • Contralateral internal carotid intervention
    • Ipsilateral external carotid intervention
    • EC-IC Bypass

N Engl J Med. 2010 May 26

Lancet. 2010 Sep 9. [Epub ahead of print]
Carotid Stenting Trialists’ Collaboration

SPARCL
(Stroke Prevention by Aggressive Reduction in Cholesterol Levels)

- 4731 patients
- recent TIA, stroke
- LDL 100-190
- Atorvastatin 80 mg vs. placebo
- First stroke
- Any CV event
- Hemorrhagic stroke significantly increased
  - HR 1.7
  - Did not cancel overall benefit


Anti-thrombotic Therapy
Secondary Prevention

- Warfarin
- Aspirin
- Clopidogrel (Plavix®)
- Aspirin-ER dipyridamole (Aggrenox®)
- Cilostazol (Pletal®)

AHA/ASA Antiplatelet Guidelines
(almost identical to European, ACCP guidelines)

- Antiplatelet agents rather than oral anticoagulation
- ASA, the combination of ASA+ER-DP, and clopidogrel monotherapy are all acceptable options for initial therapy
- ASA+ER-DP is recommended over aspirin
- Clopidogrel may be considered over ASA
- Insufficient data to make choices between antiplatelet options
- Addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended
- ASA failures, no evidence for changing

In noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation
Class I, Level of Evidence A

- Multiple RCTs – NO δ
  - WARSS NEJM 2001;345:1444-51
  - WASID NEJM 2005;352:1305-16
    - Intracranial stenosis
    - SAMMPRIS: NIH funded
  - ESPRIT Lancet Neurol 2007; 6: 115-24

Intracranial Stenosis
From: Indications for the performance of intracranial endovascular neurointerventional procedures: a scientific statement from the American Heart Association

Recommendations
1. Patients with intracranial stenoses should receive advice about lifestyle modification and treatment of atheroembolic risk factors with statins, angiotensin-converting enzyme inhibitors, and antithrombotics as recommended by the NIH/American Stroke Association guidelines for secondary stroke prevention® (Class I, Level of Evidence A).
2. Endovascular revascularization by intravascular balloon angioplasty and/or stenting may be considered for patients with symptomatic severe intracranial stenoses (>70% luminal narrowing) despite optimal medical therapy (Class IIb, Level of Evidence B).

ASA, ASA+ER-DP, and clopidogrel monotherapy are all acceptable options for initial therapy
Class I, Level of Evidence A

- Aspirin vs. Placebo RCTs
  - Bunch of old ones...
- Aspirin/dipyridamole vs. Placebo RCTs
  - ESPS1 Stroke 1990; 21:1122-1130
- Clopidogrel vs. Aspirin RCT
  - CAPRIE Lancet 1996;348:1329-39
ASA+ER-DP is recommended over aspirin
Class I, Level of Evidence B

- Aspirin/dipyridamole vs. Aspirin RCTs
  - ESPRIT Lancet 2006;367:1665-73
    - not double blinded
    - Lesser effect in “on-treatment” analysis
    - Excluded cardioembolic, carotid, disabling
- Main result consistent between trials
- Not uniform consensus among experts
- $$$$$ vs. aspirin (NNT = 104 per year)

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Clopidogrel may be considered over ASA
Class IIb, Level of Evidence B

- Clopidogrel vs. Aspirin RCT
  - CAPRIE Lancet 1996;348:1329-39
    - Main result showed slight benefit over aspirin
    - Stroke subgroup relatively equivalent efficacy
- Not uniform consensus among experts
- $$$$$ vs. aspirin

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Insufficient data to make choices between antiplatelet options

- Clopidogrel vs. ASA+ER-DP
  - PROFESS RCT, DONE
- Patient Co-morbid Characteristics
  - Aspirin failure → ASA+ER-DP vs. clopidogrel
  - Ischemic cardiac disease → clopidogrel
  - Peripheral arterial disease → clopidogrel
  - Aspirin intolerance/allergy → clopidogrel
  - Clopidogrel intolerance/allergy → asa/dipyrid.
PROFESSION

Recurrent stroke Stroke, MI, vascular death

PROFESSION Stroke event types

- ICHs increased in ASA-DP arm
- HR = 1.4 (1.1-1.8)

Network Meta-analysis

B Including Data from the PROFESSION Trial

Aspirin

Relative risk: 0.83
(95% CI: 0.81 to 1.00; P=0.08)

Aspirin-LidPl

Relative risk: 0.96
(95% CI: 0.78 to 1.13; P=0.70)

Clodipogrel

Relative risk: 0.87
(95% CI: 0.71 to 1.07; P=0.19)

From PROFESSION Trial

Direct relationship

Relative risk: 1.02
(95% CI: 0.93 to 1.11; P=0.71)

NEJM 2008;359:1287
Addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended
Class III, Level of Evidence A

- ASA vs. ASA/clopidogrel
  - CHARISMA (recent stroke, MI, or "high risk" patients)
    - NEJM 2006;354:1706-17; JACC 2007;49:1392-8
    - Increased hemorrhages
    - Failed to meet primary endpoint
      - Subgroup analyses suggest benefit of combination in stroke patients, especially if treated early
- Clopidogrel vs. Aspirin/clopidogrel
  - MATCH (recent stroke)
    - Lancet 2004;364:331-37
    - Increased hemorrhages
    - Failed to meet primary endpoint
      - Subgroup analyses suggest benefit of combination especially if treated early
- Other smaller studies: CARESS, FASTER
- Ongoing trials: SPS3, POINT

Cilostazol

- Mechanism of Action: inhibitor of phosphodiesterase III (PDE III), which causes it to be a vasodilator and inhibitor of platelet aggregation
  - But not all drugs like this work for claudication
- Other PDE III inhibitors have caused increased mortality in heart failure pts
- 1 RCT vs. placebo after stroke
- 1 pilot RCT vs. aspirin

Cilostazol for prevention of secondary stroke (CSPS 2):
an aspirin-controlled, double-blind, randomised non-inferiority trial

Lancet Neurol 2010; 9: 959-68
PFO and Cryptogenic Stroke

- More relevant in young patients without traditional vascular risk factors
- Best Rx unknown
- My approach:
  - If young, search for hypercoagulable states
  - ASA at least
  - Warfarin if high risk
    - Large PFO, atrial septal aneurysm, or multiple CVAs
  - Closure after recurrent events or if cannot tolerate meds
    - Surgery vs catheter
  - FDA IDE
  - Randomize if possible
- Trials ongoing...

Special Situations

- Dissection Stroke. 2007;38:2605-2611
  - Antiplatelets vs limited anticoagulation
- Hypercoagulable states
  - Warfarin in many cases
- Vasculitis J Neurol. 2001;248:451-468
  - Antiplatelets plus immunosuppression
- Sickle Cell Disease Lancet Neurol. 2006;5(6):501-12
  - Exchange transfusion, risk stratify by TCDs

Secondary Ischemic Stroke Prevention

<table>
<thead>
<tr>
<th>Factor</th>
<th>Rx</th>
<th>Evidence Supporting Effectiveness of Rx</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>-</td>
<td>Exercise, eat right, stop smoking</td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>-</td>
<td>ASA, RCT</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Carotid Artery</td>
<td>3-12</td>
<td>Multi RCT</td>
<td>Carotid Stenting</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 &amp; 10 yrs</td>
<td>Multi RCT</td>
<td>CEA for 25% stenosis</td>
</tr>
<tr>
<td>Aspirin</td>
<td>325 mg</td>
<td>Multi RCT</td>
<td>Minimal Rx, 1-2 yrs</td>
</tr>
<tr>
<td>Clopidogrel vs. ASA</td>
<td>-</td>
<td>1 RCT</td>
<td>Equivalent to ASA?</td>
</tr>
<tr>
<td>ASA/ER-DP vs. ASA</td>
<td>&lt; 100/yr</td>
<td>2 RCT</td>
<td>TIA/WNI patients</td>
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<tr>
<td>ASA vs. clopidogrel</td>
<td>-</td>
<td>Multi RCT</td>
<td>Stenting, subgroups</td>
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<tr>
<td>ASA/ER-DP vs. clopidogrel</td>
<td>No-b</td>
<td>1 RCT</td>
<td>Patient factors</td>
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<tr>
<td>Warfarin</td>
<td>Ineffective</td>
<td>RCT</td>
<td>Dissection, hypercoagulable states, PFO</td>
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<tr>
<td>Estrogen (HRT, vitamins)</td>
<td>Ineffective</td>
<td>RCT</td>
<td>WSS, VSP</td>
</tr>
</tbody>
</table>
STROKE IS “BRAIN ATTACK”

Time is Brain

Call 911