Secondary Stroke Prevention

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Stroke Secondary prevention

- Describe CVA subtypes
- Identify CVA Risk Factors
- Identify Signs & Symptoms of Acute Stroke
- Describe management strategies for CVA subtypes
- Describe outcomes of secondary prevention trials
  - Antiplatelets
  - Combo therapies
  - Warfarin & anticoagulants
  - Statins
  - Blood Pressure Control

- The Bottom Line!
Stroke signs

1. **Sudden** one-sided *weakness*, numbness, or paralysis of face, arm or leg.
2. **Sudden** blurry or ↓ vision.
3. **Sudden** difficulty *speaking* or understanding simple statements.
4. **Sudden** dizzy, loss of *balance* or coordination.
5. **Sudden** severe, unexplainable *headache* – “worst ...
Type Of Strokes

**Stroke Subtypes**

**Hemorrhagic Stroke (17%)**
- Intracerebral Hemorrhage (59%)
- Subarachnoid Hemorrhage (41%)

**Ischemic Stroke (83%)**
- Atherothrombotic Cerebrovascular Disease (20%)
- Cryptogenic (30%)
- Lacunar (25%)
- Small vessel disease
- Embolism (20%)

Risk Factors

- Non-Modifiable Risk Factors
## Secondary Stroke prevention

<table>
<thead>
<tr>
<th>Age</th>
<th>Prior CVA</th>
<th>FHx</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Doubling rate each decade &gt; 55 y.o.)</td>
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<table>
<thead>
<tr>
<th>Race</th>
<th>Low Birth Weight</th>
<th>Male</th>
</tr>
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<tbody>
<tr>
<td>(Blacks/Hispanics &gt; Whites)</td>
<td>(RR ~2) (Wt &lt; 2.5kg vs &gt; 4 kg)</td>
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</tbody>
</table>
Modifiable Risk Factors

- Hypertension
  - The Biggest Risk Factor!
  - ~ 28-38% Risk Reduction with Treatment
Hypertension

- Acute Phase CVA If TPA To be Administered All Pt Systolic BP Under 185
- Acute phase CVA No TPA Than Hydrate patient make Euvolemic
- A. Acute phase CVA If Chronically Hypertensive Systolic BP Permissive HTN 200+-
- In Normotensive Slow decrease to 140 systolic.
- For Chronic BP control 140-160 range all patients.
- Maintain MABP >100 \( MABP = CPP + ICP \)
- Reperfusion Achieved Assure Euvolemia SBP 160-170 MABP AT80-100
- Continued Recovery SBP 140
- CPP = MAP - ICP OR JVP which ever is greater
Modifiable risk Factors

Ischemic Heart Disease (IHD)
- CAD, CHF, LVH
- Major Risk Factor
Risk factors

- CHADS-2 model
- Score from 0 to 6, based on:
  - CHF = 1
  - High BP = 1
  - Age > 75y.o. = 1
  - Diabetes = 1
  - Stroke Hx = 2
Yearly risk of stroke due to AFib based on **CHADS-2 Score**:

- 0 - 1.9%
- 1 - 2.8%
- 2 - 4.0%
- 3 - 5.9%
- 4 - 8.5%
- 5 - 12.5%
- 6 - 18.2%
Modifiable risk factors

- **Smoking**
  - 50% Risk Reduction w/i 1 yr
  - Baseline > 5 yrs
  - Major Risk Factor!
Risk Factors

**Diabetes**
- Major Risk Factor!
- BP Control is KEY
- Mortality benefit with statins
- * No evidence that tight sugar control reduces risk of CVA
- > 140 increase morbidity by 7-10%
Dyslipidemia

25-30% Risk Reduction with statin use
Contd

- Physical Inactivity

- Heavy Alcohol use
  - > 5 drinks /day

- Obesity
Contd

- High Dose Estrogen
  - > 50 mcg /day
Asymptomatic Carotid Stenosis

- 50% Risk Reduction with endarterectomy
Carotid endarterectomy reduces stroke, but not endpoint of stroke and death, in asymptomatic men. Medical versus surgical (carotid endarterectomy) therapy in 444 men with asymptomatic carotid stenosis >50 percent. Top panel: Carotid endarterectomy reduced the four year incidence of ipsilateral stroke or TIA compared to medical therapy (6 versus 20.6 percent, P<0.001). Bottom panel: There was no difference between the two groups in the incidence of stroke and death (41 versus 44 percent) (lower panel). (Redrawn from Hobson, RW, Weiss, DG, Fields, WS, et al, N Engl J Med 1993; 328:221.)
The cumulative risk of any ipsilateral stroke at two years was 26% in the 331 medical patients and 9% in the 328 surgical patients—an absolute risk reduction 17%.
How Many US Strokes Can Be Prevented by Risk Factor Control?

- Hypertension: 360,500
- Cholesterol: 146,000
- Cigarettes: 89,500
- Atrial fibrillation: 68,500
- Heavy alcohol use: 34,500

# of Preventable Strokes Based on Estimated 700,000 Annual Strokes

Medical Therapies

- **Anti-platelets**
  - ASA
  - Clopidogrel
  - Combo Strategies
    - Clopidogrel + ASA
    - ASA + ER-Dipyridamole (Aggrenox™)
  - Ticagrelor
  - Prasugrel

- **Anti-coagulants**

- **Anti-dyslipidemics** (Statins)

- **Anti-hypertensives**
~23% RRR ASA over placebo
NNT ~ 50-100 for 1 year to prevent any vascular event.
at a dose range of 50-325mg ASA
NNH ~ 1 to 2 major extra-cranial bleeds per 1000 people
Antiplatelet Trialists

- large meta-analysis (~70% ASA trials)
- ASA 75-150mg - beneficial in all high risk patients except for those with hemorrhagic stroke.
- No added benefit of ASA 500 - 1300 mg
- BMJ 2002;324:71-86
contd

**CAST/IST Trials**

- ASA w/i 48h of CVA
- Combined analysis - significant reduction of 9 fewer deaths or nonfatal strokes per 1000 treated patients w/ ASA (160-325 mg/d)
- Absolute risk reduction (ARR) = 0.9%;
- Number needed to treat (NNT) = 111
- BMJ 1988; 296:313-16
SALT Trial – ASA 75mg vs placebo

**Bottom line** - Low dose ASA significantly reduces risk of stroke and death in patients with ischemic stroke when used for ~32 months

- **ARR** = 4.6%
- **NNT** = 22
contd

- **Antiplatelets**
  - Small differences in efficacy or toxicity, dictate that cost will drive selection.
  - = ASA
  - Combination therapy where indicated

- **Anticoagulants**
  - Small differences in efficacy
  - Important unknowns in toxicity w/ newer agents
    - (age effects, renal dysfunction, lack of antidotes)
  - Use warfarin except for carefully selected patients with *significant* compliance barriers due to the inconvenience of INR testing.
Ischemic CVA - Aggrenox or Plavix or ASA
  - If can’t tolerate one, change therapy
  - If ASA allergy - clopidogrel 75mg qd
Cardioembolic CVA - Warfarin (INR 2-3)
  - Good CrCL and poor INR control - consider Apixaban
Hemorrhagic CVA
  - If ischemic or cardioembolic transformation:
    - treat as above
  - If primary hemorrhage - usually due to HTN
    - Add ASA once acute bleed resolved (primary prevention of ischemic event)
Contd

- Ticagrelor - no improvement vs clopidogrel and possible increase in harm in stroke patients
  - PLATO study
- Prasugrel - possible improvement vs clopidogrel in ACS, but more intracranial bleeding.
  - esp. in pts with previous stroke!
  - TRITON-TIMI 38 study
<table>
<thead>
<tr>
<th>Agent</th>
<th>Monotherapy</th>
<th>Combo w/ ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>ASA ~23% RRR &gt; placebo NNT ~ 50-100 x1 year to prevent any vascular event. (50-325mg) (CAST, IST, SALT, Dutch-TIA trials)</td>
<td>--</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Superior to ASA (CATS &amp; TASS trials)</td>
<td>unknown</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Equivalent to ASA (<em>extremely</em> small absolute improvement per CAPRIE trial)</td>
<td>Possible improvement for 1&lt;sup&gt;st&lt;/sup&gt; 21 days post CVA (CHANCE trial)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No benefit long term (CHARISMA, MATCH trials)</td>
</tr>
<tr>
<td>Aggrenox®</td>
<td><em>Superior</em> to ASA (ESPRIT &amp; ESPS2 trials), but <em>Equivalent</em> to Clopidogrel (PRoFESS trial) whaa?</td>
<td>--</td>
</tr>
</tbody>
</table>
## Secondy Stroke Prevention

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ASA-ERDP (n = 10,181) # (%)</th>
<th>Clopidogrel (n = 10,151) # (%)</th>
<th>Hazard Ratio for ASA-ERDP (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major hemorrhagic event</td>
<td>419 (4.1)</td>
<td>365 (3.6)</td>
<td>1.15 (1.00-1.32)</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>128 (1.3)</td>
<td>116 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Non-life-threatening</td>
<td>291 (2.9)</td>
<td>249 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic event (minor or major)</td>
<td>535 (5.3)</td>
<td>494 (4.9)</td>
<td>1.08 (0.96-1.22)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>147 (1.4)</td>
<td>103 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>90 (0.9)</td>
<td>55 (0.5)</td>
<td>1.42 (1.11-1.83)</td>
</tr>
<tr>
<td>Fatal</td>
<td>28 (0.3)</td>
<td>29 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>62 (0.6)</td>
<td>26 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Intraocular hemorrhage</td>
<td>22 (0.2)</td>
<td>22 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Nonstroke intracranial hemorrhage</td>
<td>35 (0.3)</td>
<td>26 (0.3)</td>
<td></td>
</tr>
</tbody>
</table>
## Secondary Stroke Prevention

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ASA-ERDP 10,055 (100.0) # (%)</th>
<th>Clopidogrel (n= 10,040 (100.0) # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events leading to discontinuation</td>
<td>1,650 (16.4)</td>
<td>1,069 (10.6)</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>593 (5.9)</td>
<td>87 (0.9)</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>158 (1.6)</td>
<td>37 (0.4)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>155 (1.5)</td>
<td>58 (0.6)</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>134 (1.3)</td>
<td>52 (0.5)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>122 (1.2)</td>
<td>143 (1.4)</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>102 (1.0)</td>
<td>42 (0.4)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>54 (0.5)</td>
<td>35 (0.3)</td>
</tr>
</tbody>
</table>
3) Cost
   - **ASA**
     - Pennies!
   - **Convenience**
     - **ASA**
       - 75-325mg once daily
     - **Clopidogrel**
       - 75mg once daily
     - **Aggrenox®**
       - 200/25mg BID po
     - **Clopidogrel**
       - ~ $95/mo
       - LU code for ASA intolerance only
     - **Aggrenox®**
       - ~ $61/mo
       - LU code for CVA
<table>
<thead>
<tr>
<th>Agent</th>
<th>Cost</th>
<th>Convenience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>~ $40/mo (with INR monitoring)</td>
<td>QD po INR q3d – q1mo (ODB covered)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>$110/mo</td>
<td>BID po (ODB w/ LU code 431 for AFib)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>$100/mo</td>
<td>QD with food (ODB w/ LU codes for Afib or VTE)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>$140/mo</td>
<td>BID po (ODB w/ LU code 448 for Afib)</td>
</tr>
</tbody>
</table>
Contd

- **Warfarin**
- Vitamin K antagonist **Rivaroxaban**
- **Factor Xa** inhibitor **Rivaroxaban**
  - Factor **Xa** inhibitor

- **Apixaban**
  - **Factor Xa** inhibitor (clotting factors 2,7,9,10, protein C & S)

- **Dabigatran**
  - Direct thrombin inhibitor (factor 2)
## Anticoagulation in Non-valvular AFib

<table>
<thead>
<tr>
<th></th>
<th>COUMADIN</th>
<th>PRADAXA</th>
<th>XARELTO</th>
<th>ELIQUIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/Embolism</td>
<td>✓ 1</td>
<td>✓ 2</td>
<td>✓ 3</td>
<td>✓ 4</td>
</tr>
<tr>
<td>ICH</td>
<td>✗ 5</td>
<td>✓ 6</td>
<td>✓ 7</td>
<td></td>
</tr>
<tr>
<td>Major GI Bleed</td>
<td>✓ 8</td>
<td>✗ 9</td>
<td>✓ 10</td>
<td></td>
</tr>
<tr>
<td>Major Bleed</td>
<td>✓ 11</td>
<td>✓ 12</td>
<td>✓ 13</td>
<td></td>
</tr>
<tr>
<td>Manage Bleed</td>
<td>✓ 14</td>
<td>✗ ✗</td>
<td>✗ ?</td>
<td>✗ ?</td>
</tr>
<tr>
<td>MI</td>
<td>✓ 15</td>
<td>- ?</td>
<td>- ?</td>
<td></td>
</tr>
<tr>
<td>DC Rate/Dyspepsia</td>
<td>-</td>
<td>✗ 16</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Low renal fx CrCl</td>
<td>✓ 17</td>
<td>CI&lt;30</td>
<td>CI&lt;30</td>
<td>CI&lt;15</td>
</tr>
<tr>
<td>Cost</td>
<td>✓ 18</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Half life/Pros/Cons</td>
<td>✓ 19</td>
<td>Dosing frequency, impact of missed dose, bleed management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td>✓ 20</td>
<td>Need for/ability to monitor INR has pros &amp; cons.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certainty vs Un-</td>
<td>✓ 21</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>
Effects of Simvastatin on First Stroke

<table>
<thead>
<tr>
<th>Type of Major Vascular Event</th>
<th>Event Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strokes</td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td></td>
</tr>
<tr>
<td>Fatal stroke</td>
<td></td>
</tr>
<tr>
<td>Subtotal: any stroke</td>
<td>0.75 (0.660-0.85); RRR 25%; P&lt;.0001</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td></td>
</tr>
<tr>
<td>Coronary event, stroke, revascularization</td>
<td>0.76 (0.72-0.81); RRR 24%; P&lt;.0001</td>
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Simvastatin Better  Placebo Better

contd

- **HPS trial** - 20,596 high risk pts
- **Simvastatin 40mg vs placebo**
- **Stroke** - 4.3% vs 5.7% (RRR 25%)
- Significant regardless of age or cholesterol level!
- **Lancet 2002; 360: 23-33**
Summary

- **Cardioembolic CVA**
  - Statin, ACEinh (since likely has CHD)
  - B-blockers (CHD, also for rate control)

- **Ischemic CVA**
  - Statin; ACEinh and/or diuretic

- **Hemorrhagic CVA**
  - If primary bleed - BP control!
  - If transformation - treat as ischemic CVA once bleed resolves
Summary

- BP reduction is key!
  - Aggressive reduction
- Up to 28% reduction of second CVA
  - Up to 40-50% reduction in first CVA!
- ACEinh or Thiazides – 1st among equals?
  - Some evidence as well for ARBs
- Strongly consider ACEinh + diuretic combo
- Thank You