Evidence-Based Stroke Management: 2014 Update

Disclosures

- Research Grants
  - NIH / NINDS / NCATS (current)
  - SanBio, Inc. (stem-cell therapy for stroke not discussed)
  - American Heart Association (past, unrelated)
- No financial interests in any of the commercial entities that market any of the pharmaceuticals or devices discussed

Objectives

- Briefly review established, high-impact interventions for secondary stroke prevention
- Updates on prevention of stroke based on recent clinical evidence
  - New oral anticoagulants for stroke prevention with atrial fibrillation
    - RE-LY, ROCKET-AF, ARISTOTLE
  - Extended cardiac monitoring for cryptogenic stroke
    - EMBRACE, CRYSTAL AF
    - RESPECT-ESUS, NAVIGATE ESUS
  - Antithrombotic therapy for secondary prevention
    - FASTER, CHANCE, POINT, SOCRATES

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High-Impact Targets for Secondary Stroke Prevention

- Blood pressure, blood pressure, blood pressure
- Urgent carotid endarterectomy/stenting for symptomatic carotid stenosis
- Oral anticoagulation for atrial fibrillation
- Antiplatelet therapy
- Cholesterol-lowering therapy
- Smoking Cessation
- Alcohol

Blood Pressure: Awareness, Treatment, and Control

<table>
<thead>
<tr>
<th>Year</th>
<th>Awareness</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976-80</td>
<td>51</td>
<td>30</td>
</tr>
<tr>
<td>1988-91</td>
<td>73</td>
<td>55</td>
</tr>
<tr>
<td>1999-2000</td>
<td>68</td>
<td>56</td>
</tr>
<tr>
<td>2005-06</td>
<td>70</td>
<td>59</td>
</tr>
</tbody>
</table>

Trends in Blood Pressure in US

[Graph showing trends in blood pressure awareness, treatment, and control over time.]


### Impact of Blood Pressure on Mortality

<table>
<thead>
<tr>
<th>Reduction in SBP (mmHg)</th>
<th>% Reduction in Mortality Stroke</th>
<th>% Reduction in Mortality CHD</th>
<th>% Reduction in Mortality Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-6</td>
<td>-4</td>
<td>-3</td>
</tr>
<tr>
<td>3</td>
<td>-8</td>
<td>-5</td>
<td>-4</td>
</tr>
<tr>
<td>5</td>
<td>-16</td>
<td>-9</td>
<td>-7</td>
</tr>
</tbody>
</table>

**BP**: blood pressure; **CHD**: coronary heart disease; **SBP**: systolic blood pressure


### Age-Adjusted Mortality from Stroke

*Figure 1.* Percent decline in age-adjusted mortality rates for stroke by gender and race: United States, 1979-2000.


### Projected Stroke Deaths in US

*Figure 1.* Historical and projected total stroke deaths per year in the United States, 1979 to 2039. Projected values are the product of future age-race-sex-specific mortality rates and US Census Bureau projections.

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Evidence-Based Interventions

**Evidence-Based Interventions**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Population</th>
<th>Outcome</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV tPA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NINDS Part 1 (NEJM 1995)</td>
<td>291</td>
<td>&lt;3 hours of symptom onset</td>
<td>4 point improvement in NIHSS or resolution within 24h</td>
</tr>
<tr>
<td>NINDS Part 2 (NEJM 1995)</td>
<td>333</td>
<td>&lt;3 hours of symptom onset</td>
<td>Barthel, mRS, GOS, and NIHSS</td>
</tr>
<tr>
<td>ECASS-III (Lancet 2009)</td>
<td>821</td>
<td>3-4.5 hours of symptom onset</td>
<td>mRS &lt;2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Early Aspirin</th>
<th>Population</th>
<th>Outcome</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IST (Lancet 1997)</td>
<td>19,435</td>
<td>&lt;48 h</td>
<td>Recurrent stroke &lt;14d</td>
</tr>
<tr>
<td>CAST (Lancet 1997)</td>
<td>21,100</td>
<td>&lt;48 h</td>
<td>Mortality &lt;4 weeks</td>
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<table>
<thead>
<tr>
<th>Statin</th>
<th>Population</th>
<th>Outcome</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPARCL (NEJM 2006)</td>
<td>4,731</td>
<td>Stroke or TIA &lt;6m</td>
<td>Recurrent stroke &lt;5y</td>
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<td></td>
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<td>21,100</td>
<td>&lt;48 h</td>
<td>Mortality &lt;4 weeks</td>
</tr>
<tr>
<td>Cochrane Review (Sanderson 2008)</td>
<td>43,041</td>
<td>&lt;48 h</td>
<td>Early death or dependency</td>
</tr>
</tbody>
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Atrial Fibrillation and Stroke

- 2-3 million w/ AF in US; 12 million by 2050
- Incidence increases with age, 8% of those > 80y
- Population Attributable Risk ~ 12%
  - But strokes more severe, higher recurrence risk
- 5x higher risk; annual risk ~5% overall
  - CHADS\(_2\): CHA\(_2\)DS\(_2\)-Vasc (> 20-fold range in risk)
- 40-80% relative risk reduction w/ warfarin
  - Anticoagulation for AF underutilized
    - 50-60% of otherwise eligible patients not on appropriate anticoagulation therapy

Pharmacological Properties of New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Direct thrombin inhibitor</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td>0.5-2 h</td>
<td>3.4 h</td>
</tr>
<tr>
<td><strong>t 1/2</strong></td>
<td>12-14 h</td>
<td>12 h</td>
</tr>
<tr>
<td><strong>Renal Clearance</strong></td>
<td>80%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>P-gp inhibitors</td>
<td>P-gp inhibitors; CYP3A4</td>
</tr>
<tr>
<td><strong>Laboratory Monitoring Required?</strong></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Not crushable</strong></td>
<td>Take w/ food for bioavailability</td>
<td></td>
</tr>
</tbody>
</table>

Phase III Studies of New Oral Anticoagulants: Study Design

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>RE-LY</td>
<td>ROCKET-AF</td>
</tr>
<tr>
<td>Study Design</td>
<td>Dabigatran dose blinded; open-label warfarin</td>
<td>Double-blind, double-dummy warfarin</td>
</tr>
<tr>
<td>Intervention</td>
<td>110 mg bid 150 mg bid</td>
<td>20 mg daily 5 mg bid</td>
</tr>
<tr>
<td>Control</td>
<td>warfarin</td>
<td>warfarin</td>
</tr>
<tr>
<td>Age</td>
<td>71.5</td>
<td>73</td>
</tr>
<tr>
<td>CHADS(_2)</td>
<td>2.1</td>
<td>3.5</td>
</tr>
<tr>
<td>Hx Stroke/TIA</td>
<td>20%</td>
<td>55%</td>
</tr>
<tr>
<td>TTR*</td>
<td>64%</td>
<td>55%</td>
</tr>
</tbody>
</table>

* TTR: Time in Therapeutic Range (INR 2-3)

Phase III Studies of New Oral Anticoagulants: Major Results

<table>
<thead>
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<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>RE-LY</td>
<td>ROCKET-AF</td>
</tr>
<tr>
<td>Measure</td>
<td>RR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Non-inferior Superior (150 mg)</td>
<td>Non-inferior Superior</td>
</tr>
<tr>
<td>Stroke/systemic embolization</td>
<td>0.66 (0.53-0.82)</td>
<td>0.79 (0.66-0.96)</td>
</tr>
<tr>
<td>ICH</td>
<td>0.41 (0.28-0.60)</td>
<td>0.67 (0.47-0.93)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.93 (0.81-1.07)</td>
<td>1.04 (0.90-1.20)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.88 (0.77-1.00)</td>
<td>0.92 (0.82-1.00)</td>
</tr>
</tbody>
</table>

GI Bleeding (1.6% vs 1.2%)
GI Bleeding (3.15% vs. 2.16%)
GI Bleeding (1.1% vs. 0.5%)
GI Bleeding (0.3% vs. 0.1%)%

Note: Studies with different designs/populations/interventions: caution again making indirect comparisons
*per-protocol analysis (noninferiority)
*intention to treat analysis (superiority)
Reversal Agents

- No validated antidote available
- Activated charcoal may be helpful within a few hours of ingestion
- Dabigatran dialyzable (2/3 not protein-bound) but time to get access may be longer than half-life of drug (except in renal failure)
- Prothrombin complex concentrate (PCC)?
  - 4-factor (II, VII, IX, and X)
  - 3-factor (II, IX, X)
- Monoclonal Ab?

Other Issues

- Data limited for other indications
  - Cerebral venous sinus thrombosis
  - Hypercoagulable states
  - Valvular AF / Mechanical Heart Valves
  - Cervical artery dissection
- Adherence (missing single dose → inadequate anticoagulation) / ? Thrombolysis
- No readily available laboratory test of effect
- Drug costs ($280/month vs $6/month)
  - But may be offset by savings in monitoring costs /less ICH, better stroke outcomes
- Phase IV surveillance ongoing

Summary of Pivotal Phase III Trials

- Similar (rivaroxaban) or superior efficacy (dabigatran, apixaban) for prevention of stroke/systemic embolization compared to warfarin
- All associated with lower ICH risk compared to warfarin
- Similar (dabigatran, rivaroxaban) or lower (apixaban) major bleeding risk
  - Higher GI bleeding (dabigatran, rivaroxaban)
- Mortality benefit for apixaban
- Edoxaban (ENGAGE AF-TIMI 48, NEJM 2014)
  - FDA application pending

Use of New Oral Anticoagulants

- Consider new oral anticoagulants in patients with normal renal function that are similar to study participants
  - Previously untreated or poorly patients
  - Even with good INR control (given lower ICH rates)
- Warfarin may be preferred for
  - Severe renal insufficiency
  - Valvular AF; mechanical valves
  - Cost concerns; Poor Adherence
  - Need for quick reversal
  - Higher risk of GI bleed (for dabigatran & rivaroxaban)?
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Extended Cardiac Monitoring

- Paroxysmal AF may account for a substantial proportion of otherwise cryptogenic stroke
- Paroxysmal AF is usually asymptomatic
- Paroxysmal AF likely to be associated with similar risk of stroke as persistent AF
- Therapies to reduce stroke risk for AF are effective
- Improving detection of paroxysmal AF may identify additional candidates for anticoagulation

EMBRACE

30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event

- Study Intervention
  - 30d cardiac monitor (event loop recorder) vs. Repeat Holter monitoring (24 h)
- Population
  - 572 patients with cryptogenic ischemic stroke/TIA including 24 h ECG monitoring; 17 Canadian centers
  - Age ≥ 55 (Mean 73); 63% stroke; 38% TIA
  - Median CHADS2 score 3
- Primary endpoint
  - One or more AF or Atrial Flutter episodes lasting for ≥ 30 seconds within 90 d

EMBRACE Results

<table>
<thead>
<tr>
<th>AF ≥ 30 seconds</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>45/280 (16.1%)</td>
</tr>
<tr>
<td>Control</td>
<td>9/277 (3.2%)</td>
</tr>
<tr>
<td>Absolute Difference</td>
<td>12.9% (95% CI 8.0-17.6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AF ≥ 2.5 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Absolute Difference</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral anticoagulant prescribed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Absolute Difference</td>
</tr>
</tbody>
</table>
CRYSTAL AF
CRYptogenic STroke And underLyng AF Trial

- Study Intervention
  - Insertable (Implanted) cardiac monitor vs. standard care

- Population
  - Cryptogenic TIA/stroke (age ≥ 40 y (mean 61.5y ); no AF detected during 24h of ECG monitoring); within 90d; 447 enrolled (441 randomized) between 6/2009-4/2012

- Primary Outcome
  - Time to AF detection (>30 seconds) within 6 months

- Secondary Outcome
  - Time to AF detection (>30 seconds) within 12 months

Sanna T et al, NEJM 2014

CRYSTAL AF Results

- AF detection at 6 months
  - 8.9% in ICM group (19/221 patients)
  - 1.4% in control group (3/220 patients)
  - HR 6.4 (95% CI 1.9-21.7)
  - Median 41 days to detection (IQR 14-84)

- AF detection at 12 months
  - 12.4% in ICM group (29/221 patients)
  - 2.0% in control group (4/220 patients)
  - HR 7.3 (95% CI 2.6-20.8)
  - Median 32 days to detection (IQR 2-73)

Sanna T et al, NEJM 2014

Conclusions

- Optimal duration, modality, and appropriate patient selection for extended cardiac monitoring is not established
- Extended monitoring should be considered in patients with cryptogenic stroke
  - Detection of AF is increased by increasing the sampling period and the intensity of monitoring
  - Patients with cryptogenic stroke and subsequent detection of AF will likely benefit from anticoagulation
- ? for patients with a lower burden of AF (< 30 seconds?)
  - Is there a threshold burden of AF that confers risk of stroke and justifies anticoagulation?

Embolic Stroke of Undetermined Source (ESUS)

- Cryptogenic stroke ≈ 25% (300,000 cases in North America and Europe annually)
- ESUS Defined
  - Non-lacunar stroke by CT or MRI
  - Absence of proximal extracranial or intracranial atherosclerosis causing ≥ 50% stenosis
  - No major high-risk cardioembolic source; No other cause of stroke identified (e.g. vasculitis, dissection, drug use)
- WARSS (warfarin INR 1.4-2.8 vs. aspirin 325 mg)
  - Embolic subgroup, Recurrent stroke or death < 2y:
    - 12% warfarin vs. 18% aspirin
    - HR 0.66 (95% CI 0.4-1.2)
RE-SPECT ESUS
Randomized Evaluation in Secondary stroke PrEvention Comparing the
Thrombin inhibitor dabigatran etexilate versus acetylsalicylic acid (ASA)
in Embolic Stroke of Undetermined Source

- Study Intervention
  - Dabigatran (150 mg or 110 mg twice daily) vs.
  - Aspirin 100 mg daily

- Population
  - Age >=60 or 50-59 with one stroke RF; mRS ≤ 3
  - < 3 months after ESUS
  - ~6000 patients, 0.5-3 years of follow-up

- Primary Outcome
  - recurrent stroke or systemic embolism

- Secondary Outcomes
  - non-fatal stroke, non-fatal MI, vascular death, and all-cause death

NAVIGATE ESUS

- Study Intervention
  - Rivaroxaban 15 mg daily vs.
  - Aspirin 100 mg

- Population
  - ESUS age < 60; Event-driven sample size (555 primary outcomes); ~7000 patients; 350 sites

- Primary Outcome
  - Recurrent stroke and systemic embolization

- Secondary Outcomes
  - Cerebrovascular, cardiovascular events, mortality

Antiplatelet Cheat Sheet - Long-term

- Aspirin 50-100 mg vs. clopidogrel 75 mg vs. ER Dipyridamole/aspirin
  - Little evidence for dose-response / Generally use minimal effective dose long-term / Similar efficacy (perhaps slightly higher with clopidogrel and ER Dipyridamole/aspirin, NNT>200)
  - Clopidogrel vs. aspirin (CAPRIE)
  - ER Dipyridamole/aspirin vs. aspirin (ESPS-2, ESPRIT)
  - ER Dipyridamole/aspirin vs. clopidogrel) (PRoFESS)

- Aspirin + clopidogrel (MATCH)
  - Not recommended

Antiplatelet Cheat Sheet - Acute

- Acute Stroke Management
  - Acute aspirin 325 mg (160-300 mg) (IST, CAST)
    - Use higher dose acutely
  - Aspirin + clopidogrel (FASTER, CHANCE, POINT)
    - Consider short-term dual antiplatelet
    - SAMMPRIS
    - Asian patients x 21d
  - ER Dipyridamole/aspirin (EARLY)
    - Open-label trial; similar efficacy vs aspirin
  - Clopidogrel
    - Little current evidence to support use over aspirin acutely

9/6/2014
**CHANCE**

**Clopidogrel in High-Risk Patients with Acute Non-Disabling Cerebrovascular Events**

- **Study Intervention**
  - Clopidogrel 300 mg loading dose + 21 days clopidogrel 75 mg + open-label aspirin 75-300 mg vs.
  - Open-label aspirin 75-300 mg

- **Population**
  - 5170 patients; 114 centers in China; Minor stroke or high-risk TIA within 24h

- **Primary outcome**
  - Stroke (ischemic or hemorrhagic) within 90 days

**CHANCE Results**

- **Primary Outcome**
  - 8.2% in clopidogrel + aspirin group
  - 11.7% in aspirin group
  - HR 0.68 (95% CI 0.57-0.81)

- **Moderate or Severe Hemorrhage**
  - 0.3% in clopidogrel + aspirin group (7 patients)
  - 0.3% in aspirin group (8 patients)

**POINT**

**Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke**

- **Study Intervention**
  - Aspirin + clopidogrel 600 mg load + clopidogrel 75 mg x 90d
  - Aspirin 50-325 mg

- **Population**
  - High risk TIA (ABCD2 ≥ 4) or minor stroke (NIHSS ≤ 3) within 12 hours
  - Study ongoing (enrollment 2,285 / 5840 planned)
  - 350 international centers

- **Primary Outcome**
  - New ischemic events (ischemic stroke, MI, ischemic vascular death) within 90d

**SOCRATES**

**Acute Stroke Or Transient IsChemic Attack TReated with Aspirin or Ticagrelor and Patient Outcomes**

- **Study Intervention**
  - Ticagrelor 180 mg load + 90 mg bid vs.
  - Aspirin 300 mg load + 100mg daily

- **Patient Population**
  - >40y, minor stroke or high risk TIA within 24 hours, 10,560 planned enrollment; >500 sites

- **Primary Outcome**
  - Stroke, MI, or death < 90d

- **Secondary Outcomes**
  - Prevention of ischemic stroke within 90d
  - Net clinical outcome: stroke + MI + death + life threatening bleeding within 90d
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