“Right Medication for the Right Cardiovascular Cause of Stroke”

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Lecture Goals:

• Review the guidelines and evidence for the use of antiplatelets, anticoagulants, antihypertensives, and statins in secondary prevention of cerebral infarction
Disclosures

• Investigator: Eliquis (BMS/Pfizer), Lovenox (Sanofi)

• Speaker’s Bureau: Aggrenox (Boehringer-Ingelheim), Eliquis (BMS/Pfizer), Pradaxa (Boehringer-Ingelheim)
TIA and Stroke as Predictors of Secondary Stroke

<table>
<thead>
<tr>
<th>Time</th>
<th>Post-TIA (%)</th>
<th>Post-Stroke (%)</th>
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</thead>
<tbody>
<tr>
<td>30 days</td>
<td>4 – 8</td>
<td>3 – 10 (1 in 20)</td>
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<tr>
<td>1 year</td>
<td>12 – 13</td>
<td>5 – 14 (1 in 10)</td>
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<tr>
<td>5 years</td>
<td>24 – 29</td>
<td>25 – 40 (1 in 4)</td>
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Ischemic Stroke Mechanisms

- Small vessel lipohyalinosis (lacune)
- Large vessel atherothrombotic
  - Extracranial carotid
  - Extracranial vertebral
  - Intracranial carotid
  - Intracranial vertebral-basilar
  - Intracranial branches (ACA, MCA, PCA)
- Cardioembolic and aortoembolic
- Paradoxical embolism via PFO or pulmonary AV fistula
- Hypercoagulable states
- Other large vessel: dissection, fibromuscular dysplasia, vasculitis
- Venous
Secondary Prevention of Ischemic Stroke

What is the cause of the initial cerebrovascular event?

- Large-or small-vessel atherosclerosis
  - Antiplatelet therapy
- Unknown
- Cardioembolic
  - Anticoagulation

Warfarin-Aspirin Recurrent Stroke Study (WARSS) for non-Afib strokes

Kaplan-Meier Analyses of the Time to Recurrent Ischemic Stroke or Death According to Treatment Assignment

DAYS AFTER RANDOMIZATION

PROBABILITY OF EVENT (%)

Warfarin
Aspirin

Aspirin in Secondary Prevention of Stroke

**FDA:**
Professional labeling for aspirin recommends 50 to 325 mg/day

**ACCP:**
Aspirin recommended at 50 to 325 mg/day

- Stroke RRR 15-20%
- In stroke trials, aspirin’s effect is independent of dose between 50 to 1,500 mg/day

Prevention of Vascular Events in Stroke/TIA Patients

<table>
<thead>
<tr>
<th>Dose of Aspirin</th>
<th>Relative Risk</th>
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</thead>
<tbody>
<tr>
<td>1,000 - 1,300 mg/d</td>
<td></td>
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<tr>
<td>300 mg/d</td>
<td></td>
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<tr>
<td>50-75 mg/d</td>
<td></td>
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<tr>
<td>Overall</td>
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</table>

Clopidigrel in Secondary Stroke Prevention

- CAPRIE trial showed it effective in combined endpoint of MI, stroke, and PAD vs ASA (8.7%), but not superior to ASA in stroke
- CURE trial showed no significant reduction in stroke with ASA + clopidigrel
- MATCH and CHARISMA trials led to recommendation to avoid long term use of ASA + clopidogrel for ischemic stroke prevention
- Combination therapy “might be considered” for 90 days after non-cardioembolic ischemic stroke, low level of evidence, new recommendation in 2014
- For patients with symptomatic intracranial stenosis clopidogrel 75 mg/d added to aspirin for 90 days “might be reasonable”, low level of evidence

Relative Risk Reduction (%)

- Stroke 7.3
- MI -3.7
- PAD 23.8
- All 8.7

Aspirin better
Clopidogrel better

n = 19,185
MI = myocardial infarction
PAD = peripheral arterial disease

Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE)

- 12,562 patients enrolled with acute coronary syndromes
- Clopidogrel (300 mg loading, then 75 mg qd) + ASA (75-325 mg qd) vs. ASA (75-325 mg qd) + placebo for 3-12 months
- Primary endpoint = (CV death, MI, stroke)

<table>
<thead>
<tr>
<th></th>
<th>Clop+ASA (%)</th>
<th>Plac+ASA (%)</th>
<th>RRR (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>9.3</td>
<td>11.4</td>
<td>19.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MI</td>
<td>5.2</td>
<td>6.7</td>
<td>22.0</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>CV death</td>
<td>5.1</td>
<td>5.5</td>
<td>7.0</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.2</td>
<td>1.4</td>
<td>15.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Overall bleeding events increased by 69%

MATCH
(Plavix & ASA vs. Plavix)

• 7599 pts in 507 centers in 28 countries
• TIA (21%) or IS (79%) and HTN, DM, and/or hyperlipidemia.
• Clopidogrel 75 mg + placebo vs. Clopidogrel 75 mg + ASA 75 mg
• Ischemic events: ASA 15.7% vs placebo 16.73%, p = .244 (NS)
• Significant, life-threatening hemorrhage: ASA 2.6% vs placebo 1.3%, p < .001

CHARISMA  
(Plavix & ASA vs. ASA)

- 15,603 with clinical CV disease or multiple risks to 75 mg Plavix plus 75-162 mg/d ASA vs. 75-162 mg/d ASA
- End point was composite of MI, stroke, or CV death
- Suggestion of harm in those with just multiple risks with trend towards more events (6.6% combo vs. 5.5% ASA only, p= 0.20)
- Rate of death from CV causes significantly higher with combo (3.9% combo vs 2.2% ASA only, p=0.01)
- Bleeding rate higher in combination therapy
- Overall, Plavix + ASA not more effective than ASA alone in reducing the end point in those with symptomatic atherothromobosis
  - 6.8% with combo vs. 7.3% ASA (7% RRR but not statistically significant with P=0.22)

## Aggrenox ESPS-2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Stroke</th>
<th>Stroke or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-DP + ASA vs placebo</td>
<td>37% RRR</td>
<td>24% RRR</td>
</tr>
<tr>
<td>ER-DP vs placebo</td>
<td>16% RRR</td>
<td>15% RRR</td>
</tr>
<tr>
<td>ASA vs placebo</td>
<td>18% RRR</td>
<td>13% RRR</td>
</tr>
</tbody>
</table>
ESPS-2 Results

Stroke-Free Survival

Patients Without Stroke (%)

Time (months)

- ASA/ER-DP
- ASA
- ER-DP
- Placebo
## Stroke Prevention Therapy

An Indirect Comparison of Stroke Enrollees in CAPRIE and ESPS 2

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel vs. aspirin 325 mg/day in stroke patients (CAPRIE; 1.91 years data)(^1)</th>
<th>ASA/ER-DP vs. aspirin 50 mg/day in patients with stroke or TIA (ESPS2; 2 years data)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRR (stroke and post-stroke patients)</td>
<td>8.0% ((P = .28))*</td>
<td>23.1% ((P = .006))^2</td>
</tr>
<tr>
<td>Strokes prevented per 1,000 patients</td>
<td>8(^1)</td>
<td>30(^2)</td>
</tr>
<tr>
<td>NNT to prevent one stroke</td>
<td>121(^4)</td>
<td>34(^4)</td>
</tr>
</tbody>
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\(^3\)Albers, et al. *Chest* 2001;115(suppl):300S-320S.

\(^4\)Data on file. Boehringer Ingelheim Pharmaceuticals, Inc.
PRoFESS Trial

- 15,500 stroke patients 55 YO and older
- Enrolled within 90 days of cerebral infarction
- 21 countries and 500 sites
- Aggrenox vs. Plavix (was Plavix + ASA)
- Also compared Micardis with placebo
- Study duration 2 years

Recurrent Stroke or Intracranial Hemorrhage

* 128 of the 250 reported ICH events are also reported in the primary outcome.
Symptomatic Intracranial Stenosis

• For patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable (Class IIb; Level of Evidence B).

• For patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the data are insufficient to make a recommendation regarding the usefulness of clopidogrel alone, the combination of aspirin and dipyridamole, or cilostazol alone (Class IIb; Level of Evidence C).

• For patients with a stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, maintenance of systolic BP below 140 mm Hg and high-intensity statin therapy are recommended (Class I; Level of Evidence B).
WASID:
(Warfarin-ASA Symptomatic Intracranial Disease Trial)

• Compared Warfarin (INR 2-3) to ASA (1300 mg/d) for prevention of stroke or vascular death
• Symptomatic stenoses of ICA, MCA, VA, or BA (50-99%)
• Stopped by Safety Committee after 569 pts (800 goal): mean f/u 1.7 yrs
• Both treatments equally effective but more major hemorrhages in warfarin group
Carotid and Vertebral Dissection: CADISSS trial

• First randomized trial, just published in Feb, 2015.
• 250 patients with EC carotid or vertebral dissection treated within 7 days
• Heparin or LMWH/warfarin vs. antiplatelet (discretion of treating physician: aspirin, dipyridamole, clopidogrel, or combination) for 3 months
• Most subjects enrolled after a TIA or stroke, some just HA or Horner’s
• All 4 strokes occurred in patients with stroke as qualifying event
• Stroke or death in 3% of antiplatelet, 1% of AC patients, but P=0.63
• No deaths, one major bleed (SAH) in anticoagulation arm
• Conclusion in editorial is that stroke is quite rare after dissection and that we should abandon AC, though it could be considered for those with thrombus on angiography
• An adequately powered study would require ten thousand subjects

Lancet Neurol 2015 Feb 12; [e-pub]. Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS)
Secondary Prevention: AFib

- For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event (Class IIa; Level of Evidence C).

- VKA therapy (Class I; Level of Evidence A), apixaban (Class I; Level of Evidence A), and dabigatran (Class I; Level of Evidence B) are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in INR therapeutic range if the patient has been taking VKA therapy.

- Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF (Class IIa; Level of Evidence B).

Chronic Anticoagulation Options in NVAF

Vitamin K Antagonist- Class I; Level of Evidence A
Apixaban- Class I; Level of Evidence A
Dabigatran- Class I; Level of Evidence B
Rivaroxaban- Class Ila; Level of Evidence B
Relative risk (as compared with warfarin) in patients with NVAF

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Drug</th>
<th>Relative risk reduction and 95% CI</th>
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<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>Trifusul &amp; acenocoum</td>
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<tr>
<td></td>
<td>Clopidogrel &amp; ASA</td>
<td></td>
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<tr>
<td></td>
<td>Dabigatran 150</td>
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<tr>
<td></td>
<td>Rivaroxaban</td>
<td></td>
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<tr>
<td></td>
<td>Apixaban</td>
<td></td>
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<tr>
<td>Ischemic stroke</td>
<td>Trifusul &amp; acenocoum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clopidogrel &amp; ASA</td>
<td></td>
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<tr>
<td></td>
<td>Dabigatran 150</td>
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<td></td>
<td>Rivaroxaban</td>
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<tr>
<td></td>
<td>Apixaban</td>
<td></td>
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<tr>
<td>Major bleeding</td>
<td>Trifusul &amp; acenocoum</td>
<td></td>
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<tr>
<td></td>
<td>Clopidogrel &amp; ASA</td>
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<td></td>
<td>Dabigatran 150</td>
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<td></td>
<td>Rivaroxaban</td>
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<td></td>
<td>Apixaban</td>
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<tr>
<td>Intracranial bleeding</td>
<td>Trifusul &amp; acenocoum</td>
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<td></td>
<td>Clopidogrel &amp; ASA</td>
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<td>Rivaroxaban</td>
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<td></td>
<td>Apixaban</td>
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<tr>
<td>Gastrointestinal bleeding</td>
<td>Trifusul &amp; acenocoum</td>
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<td></td>
<td>Dabigatran 150</td>
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<td></td>
<td>Rivaroxaban</td>
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<td></td>
<td>Apixaban</td>
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Culebras A et al. Neurology 2014;82:716-724
Secondary Prevention: AFib

- The combination of oral anticoagulation (ie, warfarin or one of the newer agents) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA but is reasonable in patients with clinically apparent CAD, particularly an acute coronary syndrome or stent placement (*Class IIb; Level of Evidence C*).

- For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation **within 14 days** after the onset of neurological symptoms (*Class IIa; Level of Evidence B*).

- In the presence of high risk for hemorrhagic conversion (ie, large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhage tendency), **it is reasonable to delay** initiation of oral anticoagulation beyond 14 days (*Class IIa; Level of Evidence B*).

- The usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with ischemic stroke or TIA and AF is uncertain (*Class IIb; Level of Evidence B*).

- For patients with ischemic stroke or TIA and AF who are unable to take oral anticoagulants, aspirin alone is recommended (*Class I; Level of Evidence A*). The addition of clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable (*Class IIb; Level of Evidence B*).
Active W Study: Coumadin vs. ASA + Plavix for Stroke Prevention in Atrial Fibrillation

- 6706 patients, average follow-up 1.3 years
- INR 2-3 with warfarin vs. 75 mg Plavix and 75-100 mg ASA
- Stopped early secondary to interim finding of clear superiority of warfarin
- Annual incidence of stroke with warfarin 42% lower (1.4% vs. 2.4%)
- Major bleeding surprisingly slightly higher (not statistically significant) with Plavix + ASA (2.4%) vs warfarin (2.2%)

Cardiomyopathy

- Patients with ischemic or non-ischemic dilated cardiomyopathy are at an increased risk for stroke.

- About 10% of patients with ischemic stroke have an LV ejection fraction of < 30%

- A meta-analysis of 4 trials (n=3681) demonstrated that warfarin was associated with a 41% RRR of stroke (pooled ratio 0.59; 95% CI, 0.41-0.85; p=0.004)

- There is no available data of the use of the newer anticoagulant agents for secondary prevention of stroke in patients with cardiomyopathy.
Secondary Prevention: Hypertension

Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP $\geq 140$ mm Hg systolic or $\geq 90$ mm Hg diastolic (Class I; Level of Evidence B). Initiation of therapy for patients with BP $<140$ mm Hg systolic and $<90$ mm Hg diastolic is of uncertain benefit (Class IIb; Level of Evidence C).

Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA and are beyond the first several days (Class I; Level of Evidence A).

Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure $<140$ mm Hg and a diastolic pressure $<90$ mm Hg (Class IIa; Level of Evidence B). For patients with a recent lacunar stroke, it might be reasonable to target a systolic BP of $<130$ mm Hg (Class IIb; Level of Evidence B).

Secondary Prevention: Dyslipidemia

Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and an LDL-C level $\geq 100$ mg/dL with or without evidence for other ASCVD (Class I; Level of Evidence B).

Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, an LDL-C level $<100$ mg/dL, and no evidence for other clinical ASCVD (Class I; Level of Evidence C).
Summary: Stroke Prevention

- For non-cardioembolic stroke, anti-platelet medications are preferred
  - For long term use: aspirin alone, Plavix, or Aggrenox, base choice on cost, adverse effects, and patient preference
  - Plavix + ASA is not significantly better than ASA alone long term, and has a significantly increased bleeding rate
  - Consider Plavix + ASA for short term use following stroke with intracranial stenosis
- In atrial fibrillation, coumadin reduces stroke risk about 60% whereas ASA reduces risk only about 15%
  - The novel anticoagulants are at least as effective as coumadin, some are more effective and/or safer
- Scrupulous control of stroke risks (hypertension, diabetes, tobacco, lipids) is critical