Pharmacotherapy for Ischemic Stroke Prevention

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Disclosure

- Dr. Cohen discloses that he is a member of the speaker’s bureau for Boehringer-Ingelheim.
Epidemiology of Stroke

- 3rd leading cause of death in the USA
- 1 of every 15 deaths are due to stroke
- 750,000 strokes annually
- 150,000 deaths annually
- Most common debilitating neurologic disorder
- Of all those surviving a stroke for 3 months
  - 50% will live for 5 years and 30% will live for 10 years
  - 60% recover with self care and 20% require institutional care

Clinical Presentation of an Acute Ischemic Stroke

- Limb weakness
- Paralysis
- Hemiparesis
- Sensory complaints
  - paresthesias
  - numbness
- Facial weakness
- Aphasia
- Visual loss
- Headaches
- Seizures
- Confusion
- Lightheadedness, vertigo
- Ataxia
- Nausea and vomiting
- Photophobia
- Hearing loss
Stroke Subtypes


Modifiable Risk Factors in Ischemic Stroke

- Hypertension
  - Systolic > diastolic
- Atrial fibrillation
- Mitral stenosis or mitral annular calcification
- LAH or LVH
- History of MI
- CHF, Endocarditis
- Carotid bruits
- Prosthetic cardiac valves

- Hyperlipidemias
- Sickle Cell Disease
- Increased hematocrit
- Increased platelets
- Hyperhomocysteinemia
- Migraines
- Obesity
- Stress
- Sedentary lifestyle
Pharmacokinetics of Oral Thiazides and Thiazide-like Diuretics

<table>
<thead>
<tr>
<th>Name</th>
<th>t½ (hours)</th>
<th>Duration of effect (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>40</td>
<td>24 – 72</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>5.6 – 14.8</td>
<td>6 – 12</td>
</tr>
<tr>
<td>Indapamide</td>
<td>~ 14</td>
<td>24 – 36</td>
</tr>
<tr>
<td>Metolazone</td>
<td>nd</td>
<td>12 – 24</td>
</tr>
</tbody>
</table>

Modifiable Risk Factors Further Impact Stroke Risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Stroke Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.8x to 6x ↑</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>2x ↑</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2x ↑</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5x ↑</td>
</tr>
<tr>
<td>Exercise</td>
<td>Vigorous exercise ↓  by 14% to 18%</td>
</tr>
</tbody>
</table>
Drug-Induced Risk Factors for Ischemic Stroke

- Phenylephrine
- Pseudoephedrine
- Phenylpropanolamine
  - Cigarette Smoking
  - Risk for Women > men
- Estrogen > 50 mcg/qd
- Demulen 1/50
- Ortho Novum 1/50
- Ovcon-50
- Nelova 1/50

- Cocaine and Crack
  - Esp. men < 45-yo
- Heroin
- Amphetamines
- LSD
- PCP
- Alcohol
  - Habitual or binge

Circadian Incidence CVAs

No. of events n=1167

Marler et al, 1989
Alcohol and Ischemic Stroke
Northern Manhattan Stroke Study


TIA/Stroke Survivor’s Greatest Risk is Stroke, not MI

Recurrence of Events in Antiplatelet Trials in TIA and Ischemic Stroke Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stroke</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATS¹</td>
<td>13.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>TASS¹</td>
<td>12.5%</td>
<td>6.5%</td>
</tr>
<tr>
<td>CAPRIE¹+¹</td>
<td>10.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>ESPS-2¹</td>
<td>12.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>ATC²</td>
<td>8.3%*</td>
<td>1.7%*</td>
</tr>
</tbody>
</table>

N=1,053  N=3,069  N=6,431  N=6,602  N=22,803

*Nonfatal only
¹Stroke patient subgroup only (n = 6,431)
TIA/Stroke Survivor’s Greatest Risk is Stroke, not MI

% patients with prior stroke with a secondary ischemic event (n=225)

- 77.8%
- 20.4%

% patients with prior MI with a secondary ischemic event (n=565)

- 81.1%
- 15.2%


Secondary Prevention of Ischemic Stroke

What is the cause of the initial cerebrovascular event?

- Small or large vessel lacunar
- Unknown
- Cardioembolic

Antiplatelet therapy

Warfarin and Dabigatran
Short-term Prognosis Following Transient Ischemic Attack

Aspirin Therapy

- Dose has not been determined
  - Studies utilized 30 – 1.5g daily
- Generally doses 50 - 325 mg qd recommended
- Aspirin Triad - Bronchospasm
  - Asthma, rhinitis, nasal polyps
- High doses increases blood pressure
- Gastropathy
  - Preventable with PPIs or misoprostol
Aspirin Efficacy by Dose: Meta-Analyses in Patients With Stroke or TIA*

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>RRR (%) ± 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 – 100</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
</tr>
<tr>
<td>75 – 300</td>
<td></td>
</tr>
<tr>
<td>900 – 1500</td>
<td></td>
</tr>
<tr>
<td>650 – 1500</td>
<td></td>
</tr>
</tbody>
</table>

* Endpoint: stroke, MI, or vascular death.

Aspirin Dose and Admission for Ulcer Bleeding

<table>
<thead>
<tr>
<th>Aspirin Dose</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 mg (n=27)</td>
<td>2.3 (1.2–4.4)</td>
</tr>
<tr>
<td>150 mg (n=22)</td>
<td>3.2 (1.7–6.5)</td>
</tr>
<tr>
<td>300 mg (n=62)</td>
<td>3.9 (2.5–6.3)</td>
</tr>
</tbody>
</table>

- Bleeding risk is the same regardless of use of plain, buffered, or enteric-coated aspirin

Risk Factors for Serious Upper GI Events With NSAID Use

- Prior complicated ulcer
- Advancing age (> 65 years)
- Concomitant anticoagulant use
- Concomitant corticosteroid use
- Concomitant aspirin use (including low-dose)
- Concomitant SSRI use
- Multiple NSAID use
- High-dose NSAIDs
- Selection of NSAID (eg, etodolac or nabumetone vs ketorolac, indomethacin, or piroxicam)


SSRIs and NSAIDs Pharmacodynamic Drug Interactions

Case-control analysis:
11,261 cases of GI bleeding and 53,156 controls

<table>
<thead>
<tr>
<th>Odds Ratio for GI bleeding</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any NSAID alone</td>
<td>2.15</td>
</tr>
<tr>
<td>Any SSRI alone</td>
<td>2.38</td>
</tr>
<tr>
<td>NSAID + SSRI</td>
<td>2.93</td>
</tr>
</tbody>
</table>

Study suggests that the risk of GI bleeding is not substantially increased during concomitant NSAID and SSRI use compared with their use alone

Aspirin Dosage: Not All Patients Are Created Equal

Aspirin-Resistant Population
Up to 25% of Aspirin Users Are Resistant
Only the higher doses of aspirin may be efficient for CV prevention in certain patients.

Ibuprofen interferes with aspirin access to the serine binding site

**CAPRIE Study Design**

**CAPRIE: Efficacy of Clopidogrel vs Aspirin in MI, Ischemic Stroke, or Vascular Death**

- **Prospective, randomized, blinded**
- **19,185 patients with atherosclerotic vascular disease**
- **Recent ischemic stroke (≤6 mo.)**
- **Recent MI (≤35 d)**
- **Established peripheral arterial disease**
- **Clopidogrel bisulfate: 75 mg qd**
- **Aspirin: 325 mg qd**
- **Up to 3 yrs (mean 1.6 yr)**
- **304 in 16 countries, including the US**

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*ITT analysis.*

CAPRIE: Results for Patient Subpopulations

Relative Risk Reduction (%) for combined end point of stroke MI or vascular death

Stroke 7.3
MI -3.7
PAD 23.8
Combined 8.7

-40
Aspirin better
40
Clopidogrel better

A test of heterogeneity was statistically significant (p=0.042)


CAPRIE: Safety

<table>
<thead>
<tr>
<th>% Patients</th>
<th>Clopidogrel (n=9,599)</th>
<th>Aspirin (n=9,569)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigestion/nausea/vomiting</td>
<td>15.0</td>
<td>17.6*</td>
</tr>
<tr>
<td>GI hemorrhage</td>
<td>2.0</td>
<td>2.7*</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.5*</td>
<td>3.4</td>
</tr>
<tr>
<td>Rash</td>
<td>6.0*</td>
<td>4.6</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>3.0</td>
<td>3.2*</td>
</tr>
<tr>
<td>Any bleeding disorder</td>
<td>9.3</td>
<td>9.3</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*p<0.05

## Management of Atherothrombosis with Clopidogrel in High-risk Patients (MATCH): Trial Design

<table>
<thead>
<tr>
<th>Study design</th>
<th>507 clinical centers in 28 countries; randomized, double-blind, placebo-controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>7,599 patients (\geq) 40 yr (mean age 66.3 yr) with recent (within 90 days of study entry) TIA or ischemic stroke and a high risk of recurrent ischemic events</td>
</tr>
<tr>
<td>Study drugs</td>
<td>Clopidogrel (75 mg/day) plus aspirin (75 mg/day) vs. clopidogrel (75 mg/day) plus placebo</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Ischemic stroke, MI, vascular death or rehospitalization for acute ischemic event or urgent revascularization or TIA</td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td>Outcome clusters of primary endpoints, any death or any stroke</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>Treatment and follow-up period 1.5 yr</td>
</tr>
</tbody>
</table>


## MATCH: Number of Patients with Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Clopidogrel (n=3,802)</th>
<th>Clopidogrel + ASA (n=3,797)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>319 (8.4%)</td>
<td>299 (7.9%)</td>
</tr>
<tr>
<td>MI</td>
<td>62 (1.6%)</td>
<td>59 (1.6%)</td>
</tr>
<tr>
<td>Other CV Death</td>
<td>74 (1.9%)</td>
<td>69 (1.8%)</td>
</tr>
<tr>
<td>Death</td>
<td>181 (4.8%)</td>
<td>169 (4.5%)</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All results not statistically significant.

MATCH: Safety

Bleeding Complications

- Clopidogrel (n=3,781)
- Clopidogrel + ASA (n=3,759)

<table>
<thead>
<tr>
<th>Minor</th>
<th>Major</th>
<th>Life-threatening</th>
<th>Major + Life-threatening</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>96</td>
<td>71</td>
<td>169</td>
<td>289</td>
</tr>
<tr>
<td>1.0%</td>
<td>2.6%</td>
<td>1.9%</td>
<td>4.5%</td>
<td>7.7%</td>
</tr>
<tr>
<td>3.2%</td>
<td>0.6%</td>
<td>1.3%</td>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>73</td>
<td>49</td>
<td>110</td>
<td></td>
</tr>
</tbody>
</table>

p<0.0001 for all hemorrhagic complications categories.

Atorvastatin Reduces the Ability of Clopidogrel to Inhibit Platelet Aggregation

- Clopidogrel is an inactive prodrug
  - 85% hydrolyzed to an inactive carboxylic acid
  - 15% via CYP3A4 to an active metabolite
- Atorvastatin is a CYP3A4 substrate
  - Not a known CYP inhibitor
STUDY 1

**Clopidogrel**
- (n=16)  
  - 92±5  
  - p < 0.0001

**Clopidogrel + Pravastatin**
- (n=9)  
  - 34±23  
  - p < 0.0001

**Clopidogrel + Atorvastatin**
- (n=19)  
  - 77±15  
  - p = ns

**Atorvastatin Dose**
- 0 mg  
  - 34±23  
  - p = 0.002

- 10 mg  
  - 58±15  
  - p = 0.001

- 20 mg  
  - 74±10  
  - p = 0.027

- 40 mg  
  - 89±7  
  - p = 0.001

**p = 0.027**
- 0 mg  
  - 34±23  
  - p = 0.002

**p = 0.001**
- 10 mg  
  - 58±15  
  - p = 0.027

**p = 0.027**
- 20 mg  
  - 74±10  
  - p = 0.001

**p = 0.001**
- 40 mg  
  - 89±7  
  - p = 0.027
Clopidogrel Metabolism

**Clopidogrel**

Hydrolysis 85%

CYP-3A4

Inactive Carboxylic Acid Derivative

CYP-2C19

2-oxo-clopidogrel Thiol

P2Y12 inhibitory G-protein coupled Receptor is target of ADP-Inhibitors

Alleles

G52T

C139T

T744C

C34T (4-fold higher risk of stroke)

Adverse Outcomes Associated With Clopidogrel and PPI following ACS

- Retrospective VA study in 127 centers
- 8205 ACS patients followed after discharge; omeprazole and rabeprazole studied
- Chart reviews and pharmacy records for 30 months
- No misclassification bias

<table>
<thead>
<tr>
<th>Outcome following hospital discharge for ACS</th>
<th>Clopidogrel (n = 2961)</th>
<th>Clopidogrel + PPI (n = 5244)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or Rehospitalization</td>
<td>20.8%</td>
<td>29.8%</td>
<td>1.25 (1.11-1.41)</td>
</tr>
<tr>
<td>Rehospitalization for ACS</td>
<td>6.9%</td>
<td>14.6%</td>
<td>1.86 (1.57-2.20)</td>
</tr>
<tr>
<td>Revascularization Procedures</td>
<td>11.9%</td>
<td>15.5%</td>
<td>1.49 (1.30-1.71)</td>
</tr>
<tr>
<td>Death (all cause)</td>
<td>16.6%</td>
<td>19.9%</td>
<td>0.91 (0.80-1.05)</td>
</tr>
</tbody>
</table>

Ho MP, et al. JAMA. 2009;301937-944
Elimination Profiles of Substrate Drugs

<table>
<thead>
<tr>
<th>PPI</th>
<th>Elimination</th>
<th>2C19 Inhibitory Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole</td>
<td>2C19 (80%) and 3A4</td>
<td>++</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>2C19 (80%) and 3A4</td>
<td>+++</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>2C19 and 3A4 (unknown percentages)</td>
<td>++++++</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>2C19 and 3A4 (unknown percentages)</td>
<td>+++</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>2C19 (main) and 3A4 (unknown percentages)</td>
<td>+</td>
</tr>
<tr>
<td>H-2 Antagonists</td>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Metabolized in GI Tract; 80% renal</td>
<td></td>
</tr>
<tr>
<td>Dipyridamole ER/ASA</td>
<td>Glucuronidation</td>
<td></td>
</tr>
</tbody>
</table>


CYP450-2C19 Polymorphisms

- CYP-2C19*1 is the active wild type allele
  - Extensive metabolizers
- CYP-2C19*2 and CYP-2C19*3 are inactive variant alleles
  - 30% Asians are poor metabolizers (PMs)
  - 10% African Americans PMs
  - 5% Caucasians are PMs
  - *2 is found in 13% of Caucasians
  - *2 is found 35% of Asians
  - *3 is found in almost all Asians
  - *3 rare in Caucasians
Clopidogrel Dosing Strategies for 2C19 PMs

- Boxed Warning (March 2010)
  - 50% decreases in activity
  - Tests to identify 2C19 variant alleles are available
- Poor Metabolizers (2C19*2 or *3)
  - 600 mg LD
  - 150 mg daily

ESPS-2: Study Design

- Multicenter, randomized, double-blind, placebo-controlled trial
- 6,602 patients randomized within 3 months of qualifying event (TIA or stroke)
- Treatment and follow-up time: 2 years
  - Visits at 1 month and 3 months, then at 3-month intervals

ESPS-2: Treatment Arms

N = 6,602

- Placebo (n = 1,649)
- ASA 25 mg bid (n = 1,649)
- ER-DP 200 mg bid (n = 1,654)
- ASA/ER-DP 25 mg ASA/200 mg ER-DP bid (n = 1,650)

ESPS-2 Results: Cumulative Stroke Rate

Relative Risk Reduction

- Placebo
- ER-DP
- ASA
- ASA/ER-DP

22% \(P=0.008\)
37% \(P<0.001\)
ESPS-2 Results: RRR for All Strokes

![Graph showing RRR vs Placebo (%)]

**ASA ER-DP**
- **18.9%** $P = 0.009$
- **16.5%** $P = 0.036$

**ASA/ER-DP**
- **36.8%** $P < 0.001$

ESPS 2:
ASA/ER-DP Significantly Reduces the Risk of Stroke over ASA Alone

![Bar chart showing total number of events (2-year follow-up)]

**ASA** (n=1,649)
- Stroke (23% RRR): 206, 12.5%
- MI (13% RRR): 39, 2.4%

**ASA/ER-DP** (n=1,650)
- Stroke (23% RRR): 157, 9.5%
- MI (13% RRR): 35, 2.1%

*p=0.006
ESPS 2: Safety

Aspirin and Extended Release Dipyridamole

- A combination extended release gelatin capsule containing a DP:ASA ratio of 8:1
  - 200 mg extended release dipyridamole bid
  - 25 mg immediate release ASA bid
  - Combo is more effective than either agent alone
- The inhibition of adenosine uptake is dose dependent at levels of 0.5 – 2 mcg/mL
- Cmax = 2 mcg/mL; Cmin = 0.5 mcg/mL

<table>
<thead>
<tr>
<th></th>
<th>ER-DP (%)</th>
<th>ASA (%)</th>
<th>ASA + ER-DP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>37.2*</td>
<td>33.1</td>
<td>38.2</td>
</tr>
<tr>
<td>GI complaints</td>
<td>30.5</td>
<td>30.4</td>
<td>32.8+</td>
</tr>
<tr>
<td>Dizziness</td>
<td>30.1</td>
<td>29.2</td>
<td>29.5</td>
</tr>
<tr>
<td>Bleeding (any site)</td>
<td>4.7</td>
<td>8.2*</td>
<td>8.7*</td>
</tr>
<tr>
<td>Severe or fatal bleeding</td>
<td>0.4</td>
<td>1.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*p<0.001 compared with placebo
+*p=0.042 compared with placebo

ASA and ER Dipyridamole Pharmacokinetics

- 99% bound to albumin and alpha-1 acid glycoproteins
- $T_{1/2} = 13$ hours
- Dipyridamole is released over 7 – 8 hours
- Dipyridamole is eliminated via conjugation and glucuronidation
  - Monoglucuronide metabolite is weak
  - Negligible renal elimination

Aspirin and Extended Release Dipyridamole

- Extended release and not prompt release product is effective and recommended
  - Tartaric acid in ER product
  - 50% increase in bioavailability
- Dipyridamole 75 – 100 mg indicated as an adjunct to warfarin for prevention of postoperative thromboembolic complications of cardiac valve replacement
- The aspirin in this product may not be enough to treat cardiac indications (50 mg)
- Dipyridamole is a potent vasodilator
  - Chest pain in patients with unstable angina

"Results: Headache episodes, being mostly mild and transient, rapidly declined from 67% of the volunteers on the first day of treatment to 3% on the final days of treatment."
Ticlopidine Adverse Effects

- Bleeding incidence similar as with ASA
- Diarrhea
- Neutropenia
- Elevated LETs
  - Contraindicated with severe liver impairment
- Increases cholesterol and triglycerides by 10%
  - Effect is persistent throughout therapy
- Rash +/- pruritus and may progress to SJS/TEN
  - Onset is 11 days; occurs within 3 months

Ticlopidine and Clopidogrel-Induced Thrombotic Thrombocytopenic Purpura (TTP)

- Mechanism: autoantibodies (IgG) against a metalloprotease that degrades von Willebrand factor resulting in platelet microthrombi
- 1:1,600-4,000 with ticlopidine
  - Onset 3 – 4 weeks
- Many case reports with clopidogrel
  - 4 cases:1 million patients exposed
  - Onset 2 weeks
## Ticlopidine and Clopidogrel-Induced TTP

- **Life-threatening**
  - Up to 30% mortality
- Treatment is supportive and plasma exchange
- **Presentation**
  - Thrombocytopenia
  - Hemolytic anemia
  - Renal dysfunction
  - Neurologic changes

- **Fever**
- Weakness or/and pallor
- Purpura or Petechiae
- Dark urine
- Seizures
- Dysarthria
- Jaundice
- **Schistocytes on smear**

### Blood Smear With Cell Fragmentation (Schistocytes) & Thrombocytopenia

![Blood Smear With Cell Fragmentation](image)
Antiplatelet Agents vs Aspirin: Prevention of Stroke - Indirect Comparison Across Studies

* Statistically significant.
Adapted from Albers et al. *Chest*. 1998;114:683S.

Conclusions

- All patients with a non-cardioembolic stroke or TIA should receive an antiplatelet agent
- Initial choice may be:
  - Aspirin 50 – 325 mg
  - Aspirin/Dipyridamole ER
  - Clopidogrel
- ASA/ER DP is more effective than ASA (grade 1A)
- Clopidogrel is recommended in favor of ticlopidine because of a safer side effect profile
- Clopidogrel has not been shown to be more effective than ASA
- Clopidogrel plus aspirin for stroke prevention is not recommended