Controversies in Thrombosis Prevention: Update on Antiplatelet and Anticoagulant Therapies

Tuesday, June 8, 2010
8:00 a.m. – 10:00 a.m.

Overview of New Antiplatelet and Anticoagulant Drugs

Joel C. Marrs, PharmD, BCPS, CLS
Assistant Professor
University of Colorado
June 8, 2010

Disclosures
The presenters for this continuing pharmacy education activity report no relevant financial relationships except:
• Robert Lee Page II - Member of speaker's bureau for Astra Zeneca

Learning Objectives
• Define the latest issues in antiplatelet and anticoagulation therapy.
• Recommend appropriate therapy using aspirin for the primary prevention of myocardial infarction (MI) in specified cases.
• Identify and correct complications involving clopidogrel interactions in specified cases.
• Identify potential roles in therapy for newer antiplatelet and anticoagulant therapies.

Antiplatelet Therapies
• Oral Antiplatelet Therapy
  – Aspirin
  – Thienopyridines (ADP receptor/P2Y12 inhibitors)
    • ticlopidine
    • clopidogrel
    • prasugrel
    • ticagrelor
• Intravenous Glycoprotein IIb/IIIa Inhibitors
  – abciximab
  – eptifibatide
  – tirofiban

Antithrombotic Therapies
• Oral Factor Xa Inhibitor
  – Dabigatran
  – Apixaban
  – Rivaroxaban
  – Edoxaban
• Intravenous Glycoprotein IIb/IIIa Inhibitors
  – Tirofibran
  – Abciximab
  – Eptifibatide
  – Tirofiban

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ADP Receptor Antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ticlopidine</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability (%)</td>
<td>80-90</td>
<td>&gt;50</td>
<td>80-100</td>
<td>NA</td>
</tr>
<tr>
<td>Protein Binding (%)</td>
<td>98</td>
<td>94-98</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>12.6</td>
<td>7.8</td>
<td>3.7</td>
<td>12</td>
</tr>
<tr>
<td>Metabolism</td>
<td>90% hepatic; no active metabolites</td>
<td>Hepatic active metabolites</td>
<td>Hepatic active metabolites; 70% renal</td>
<td>Oral active metabolites</td>
</tr>
<tr>
<td>Onset of antiaggregation</td>
<td>&lt; 4 days</td>
<td>2 hours</td>
<td>0.5 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td>Steady state of antiaggregation</td>
<td>8-11 days</td>
<td>3-7 days</td>
<td>3 days</td>
<td>2-3 days</td>
</tr>
<tr>
<td>FDA approval</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Phase III</td>
</tr>
<tr>
<td>Reversibility</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>+</td>
</tr>
</tbody>
</table>

NA = not available

Thromb Haemost 2010;103:496-506.

Thienopyridine Biotransformation

Anticoagulant Therapies

- Oral Direct Thrombin Inhibitors
  - dabigatran
- Oral Direct Factor Xa Inhibitors
  - apixaban
  - rivaroxaban
- Vitamin K Antagonist
  - warfarin

- Heparin
  - UFH
  - LMWH
    - dalteparin
    - enoxaparin
- IV Direct Thrombin Inhibitors
  - hirudin
  - bivalirudin
  - argatroban
- Pentasaccharides
  - fondaparinux

Antithrombotic Therapies

- Aspirin
- Thienopyridines
- Oral Factor Xa Inhibitors
- LMWH
- Fondaparinux
- Warfarin

New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Thrombin</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>90</td>
<td>66</td>
<td>7.2</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>3.2-9.1</td>
<td>8-15</td>
<td>7.1-17</td>
</tr>
<tr>
<td>Metabolism</td>
<td>66% fecal; 33% renal</td>
<td>75% fecal; 25% renal</td>
<td>20% fecal; 80% renal</td>
</tr>
<tr>
<td>Elimination pathway</td>
<td>50% unchanged; 50% inactive metabolites</td>
<td>70% unchanged; 30% inactive metabolites</td>
<td>100% unchanged; active metabolites</td>
</tr>
<tr>
<td>Substrate of CYP enzymes</td>
<td>Yes (3A4, 2J2)</td>
<td>Yes (3A4)</td>
<td>No</td>
</tr>
<tr>
<td>FDA approval</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

CYP = cytochrome P450

Controversies in Thrombosis Prevention: Update on Antiplatelet and Anticoagulant Therapies

ACUTE MANAGEMENT

Robert L. Page II, Pharm.D., MSPH, FCCP, FAHA, FASHP, FASCP, CGP, MSPH, FCCP, FAHA, FASHP, FASCP, CGP
Associate Professor
Clinical Specialist, Division of Cardiology/Heart Transplant
University of Colorado Denver, Schools of Pharmacy & Medicine

Aspirin Response

JACC 2004; 43(6): 1122

Clopidogrel Response

JACC 2006; 48(2): 298

Diabetes 2005; 54(8): 2430

Clopidogrel Variability

Modified from JACC 2007; 49(14): 1505-16.

Clinical Case

75 yo woman presents to ER with NSTEMI. PHM: hypertension, dyslipidemia, diabetes, GI bleed
Meds: lisinopril 10 mg daily, atrovastatin 40 mg daily, glipizide 10 mg daily, aspirin 81 mg daily
Cardiology team tells you to load the patient with clopidogrel prior to PCI. What doses do you use?
Definite Stent Thrombosis within the Four Groups

Clinical Case

Our 75 year old woman has now undergone PCI with 2 drug-eluting stents. She is being discharged on the following: metoprolol 25 mg po BID, aspirin 325 mg po daily, clopidogrel 75 mg daily, lisinopril 40 mg daily, glipizide 10mg BID, atorvastatin 80 mg daily.

BUT….you remember something about a controversy regarding PPIs-Clopidogrel…what do you do?
**ACC-AHA-ACG Joint Statement**

October 2008

- Recommendation: PPIs are the preferred agents for the therapy and prophylaxis of NSAID- and ASA-associated GI injury.
- Traditional doses of H2-receptor antagonists (H2RAs) do not prevent most NSAID-related gastric ulcers (although high doses may be better).

Modified from http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.108.191087v1

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**Hospital Data: Bleeding**


- GI = gastrointestinal; HR = hazard ratio; PPI = proton-pump inhibitor.
- * Rate is per 1000 person-years. Analysis by PPI dose and individual drug excludes person-time with concurrent use of multiple PPIs.

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**Hospital Data: CV Events**


- AMI = acute myocardial infarction; CV = cardiovascular; CVD = cardiovascular disease; HR = hazard ratio; PPI = proton-pump inhibitor; 2013 = updated decision science.
- * Rate is per 1000 person years. Analysis by PPI dose and individual drug excludes person-time with concurrent use of multiple PPIs.

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**BUT WAIT....AGAIN**

ACC 2010 Scientific Meeting. Atlanta, GA

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**Bottom Line**

1. Patients on PPIs should only receive a PPI for a solid indication. Consider antacids and H-2 blockers when appropriate.

2. Prasugrel…but be careful of patient characteristics.

3. Coming down the pipeline… ticagrelor

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**Death from CV Causes, Nonfatal MI, Stroke**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Prasugrel N=13,457</th>
<th>Clopidogrel N=13,457</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death 24 mo. from CV causes or MI</td>
<td>0% (95% CI: 0.0-0.3%)</td>
<td>2.4% (95% CI: 1.5-3.3%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Death 24 mo. from CV causes</td>
<td>0.1% (95% CI: 0.0-0.2%)</td>
<td>1.2% (95% CI: 0.6-2.0%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Death 30 mo. from CV causes or MI</td>
<td>0.7% (95% CI: 0.2-1.3%)</td>
<td>1.2% (95% CI: 0.6-2.0%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Death 30 mo. from CV causes</td>
<td>0.0% (95% CI: 0.0-0.1%)</td>
<td>0.7% (95% CI: 0.3-1.4%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Non-CVA major bleeding (n=13,916)</td>
<td>6.0% (95% CI: 5.1-6.9%)</td>
<td>6.6% (95% CI: 5.8-7.5%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Non-CVA major bleeding (n=13,362)</td>
<td>5.6% (95% CI: 4.8-6.4%)</td>
<td>6.2% (95% CI: 5.4-7.0%)</td>
<td>0.10</td>
</tr>
<tr>
<td>TIMI Major Bleeds (n=13,457)</td>
<td>0.4% (95% CI: 0.3-0.5%)</td>
<td>0.6% (95% CI: 0.5-0.7%)</td>
<td>0.03</td>
</tr>
<tr>
<td>TIMI Major Bleeds (n=13,362)</td>
<td>0.4% (95% CI: 0.3-0.5%)</td>
<td>0.6% (95% CI: 0.5-0.7%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Events, %**

- 1.8
- 2.4
- 0.9
- 1.4
- 0.9
- 1.1
- 0.3
- 0.3
- 0.1
- 0.4
- 0.3

**Safety Cohort (N=13,457)**

- TIMI Major Bleeds
- Life Threatening
- Nonfatal
- Fatal
- ICH

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**Subgroup Analysis on ARC Stent Thrombosis**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;75 yrs</td>
<td>1.6% (95% CI: 1.2-2.1%)</td>
<td>2.7% (95% CI: 2.0-3.4%)</td>
</tr>
<tr>
<td>Age ≥75 yrs</td>
<td>2.2% (95% CI: 1.6-2.9%)</td>
<td>3.0% (95% CI: 2.3-3.8%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.8% (95% CI: 1.3-2.4%)</td>
<td>2.8% (95% CI: 2.0-3.7%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.6% (95% CI: 1.2-2.1%)</td>
<td>2.7% (95% CI: 2.0-3.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.8% (95% CI: 1.3-2.4%)</td>
<td>2.8% (95% CI: 2.0-3.7%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.6% (95% CI: 1.2-2.1%)</td>
<td>2.8% (95% CI: 2.0-3.7%)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1.8% (95% CI: 1.3-2.4%)</td>
<td>2.8% (95% CI: 2.0-3.7%)</td>
</tr>
<tr>
<td>Prior Stroke/TIA</td>
<td>1.6% (95% CI: 1.2-2.1%)</td>
<td>2.7% (95% CI: 2.0-3.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>1.8% (95% CI: 1.3-2.4%)</td>
<td>2.8% (95% CI: 2.0-3.7%)</td>
</tr>
</tbody>
</table>

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**Modified from The Lancet. 2008;371:1353-1363.**
**Ticagrelor**

Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- **Direct acting**
  - Not a prodrug: does not require metabolic activation
  - Rapid onset of inhibitory effect on the P2Y12 receptor
  - Greater inhibition of platelet aggregation than clopidogrel

- **Reversibly bound**
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel

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**Clinical Case**

Our 70 year old woman has now undergone PCI with 2 drug-eluting stents. She is being discharged on the following:

- metoprolol 25 mg po BID, aspirin 325 mg po daily, clopidogrel 75 mg daily, lisinopril 40 mg daily, esomeprazole 20 mg daily, glipizide 10mg BID, atorvastatin 80 mg daily.

Now our patient has developed atrial fibrillation. It is decided that to rate control this patient but what about anticoagulation...our patient doesn’t want to take “rat poison.”
**Anticoagulation in AF**

*Stroke Risk Reductions*

- Warfarin Better
- Control Better

**CHADS2 Risk Stratification Scheme**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Recent congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S2 History of stroke or transient ischemic attack (TIA)</td>
<td>2</td>
</tr>
</tbody>
</table>

**CHADS2 Risk Criteria for Stroke in Nonvalvular AF**

<table>
<thead>
<tr>
<th>Patients (N=1733)</th>
<th>CHADS2 Score</th>
<th>Adjusted Stroke Rate (%)/y</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>463</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>523</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>337</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>220</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

**ACTIVE-W: Cumulative Risk of Stroke**

- **RR=1.72 (1.24-2.37), P=.001**
- Clopidogrel + aspirin
- Oral anticoagulation therapy

**Warfarin for Atrial Fibrillation**

*Limitations Lead to Under-treatment*

- Overall Use: 55%
- Age (years):
  - <55: 44%
  - 55-64: 58%
  - 65-74: 61%
  - 75-84: 57%
  - ≥85: 35%
**ACTIVE-A: Cumulative Risk of Stroke**

![Graph showing cumulative risk of stroke with Aspirin and Clopidogrel+Aspirin](New England J Med. 2009;360:2066-2078)

**Clinical Case**

Our 70 year old woman has now undergone PCI with 2 drug-eluting stents. She is being discharged on the following:
- Metoprolol 25 mg po BID
- Aspirin 325 mg po daily
- Clopidogrel 75 mg daily
- Lisinopril 40 mg daily
- Glipizide 10mg BID
- Atorvastatin 80 mg daily

The medical team wants to know what are the newest agents to replace warfarin.

**RELY: Dabigatran**

![Graph showing stroke or systemic embolism with Dabigatran and Warfarin](Modified from NEJM 2009;361:1139-51)

**ARISTOTLE: Apixaban**

Atrial fibrillation with at least 1 additional risk factor for stroke

Randomize
Double blind (N = 15000)
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- CHF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Apixaban 5 mg oral, b.i.d.
Apixaban placebo, b.i.d.
Warfarin placebo
Warfarin (target INR 2-3)

Warfarin/warfarin placebo adjusted INR/sham INR based on encrypted point-of-care testing device

Primary outcome: stroke and systemic embolism
Other outcomes: death, MI, bleeding
Stratified by warfarin-naive status
448 events over anticipated 2 year median followup;
>95% power to show non-inferiority (apixaban vs warfarin upper bound of 95% CI <1.38)

http://clinicaltrials.gov/ct2/show/NCT00412984

*Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation*

**ROCKETAF: Rivaroxaban**

AF

Randomized
Double blind/Double dummy (N ~ 14000)

Rivaroxaban
20 mg daily

Warfarin
(target INR: 2.5; 2-3 inclusive)

Monthly monitoring and adherence to standard of care guidelines

Primary outcome: stroke and non-CNS systemic embolism
Statistics: non-inferiority, >95% power, 2.3% warfarin event rate

*Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation*
Controversies in Thrombosis Prevention: Update on Antiplatelet and Anticoagulant Therapies

Tuesday, June 8, 2010
8:00 a.m. – 10:00 a.m.

Chronic Anticoagulation and Antiplatelet Pharmacotherapy

Joel C. Marrs, PharmD, BCPS, CLS
Assistant Professor
University of Colorado
June 8, 2010

Learning Objectives

• Define the latest issues in antiplatelet and anticoagulation therapy.
• Recommend appropriate therapy using aspirin for the primary prevention of myocardial infarction (MI) in specified cases.
• Identify and correct complications involving clopidogrel interactions in specified cases.
• Identify potential roles in therapy for newer antiplatelet and anticoagulant therapies.

Chronic Anticoagulation (Atrial Fibrillation)

• Why do we need an alternative to warfarin?
• What do the guidelines tell us?
• Do we have any data on new oral anticoagulants in atrial fibrillation yet?
• What is the data on pharmacist run anticoagulation clinics?

Vignette

HPI: TF is a 70 yof who is presenting to clinic for a follow-up visit to get her INR checked. She is frustrated by needing to come into clinic every 2-3 weeks since last being hospitalized 3 months ago to have her INR checked. She wants to go off of the warfarin because of the monitoring.

PMH: STEMI (2 stents placed 3 month ago)
Atrial Fibrillation (chronic)
Hypertension
Dyslipidemia
Social Hx: (-) tobacco; (-) ETOH

Current medications include: All: NKDA
metoprolol tartrate 50 mg po bid
warfarin 5mg MWF, 7.5 mg all other days
simvastatin 40mg po qhs
lisinopril 20 mg po daily
aspirin 81 mg po daily
clopidogrel 75 mg po daily

Vitals/Labs today at clinic are as follows:
BP 130/85, HR 70, RR 25, Ht 5’7”, Wt 150 lbs
INR = 2.2
Questions

Do the CHEST guidelines indicate this patient for chronic warfarin therapy?

What is the patients’ CHADS2 Score?

Limitations to Vitamin K Antagonists

- Slow onset and offset of action
- Narrow therapeutic index
- Variable and unpredictable anticoagulation effects due to
  - Genetic polymorphisms of CYP P450 2C9 and VKORC1* genes
  - Multiple drug and food interactions
  - Concurrent disease states
- Need for monitoring of anticoagulant effects and dose adjustments

* Vitamin K epoxide reductase complex subunit 1 (VKORC1)

ACCP 2008 Recommendations for Stroke Prevention (CHEST)

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any high risk factor or ≥2 moderate risk factors</td>
<td>Warfarin (INR 2-3 or 2.5-3.5 if mechanical valve) (1A)</td>
</tr>
<tr>
<td>One moderate risk factor</td>
<td>Warfarin (INR 2-3) (1A) or ASA 75 to 325mg QD (1B)</td>
</tr>
<tr>
<td>No Risk factors and age &lt;75</td>
<td>ASA 75 to 325 mg QD (1B)</td>
</tr>
</tbody>
</table>

Trial Data (New Anticoagulants)

- Dabigatran – RE-LY (completed)
- Apixaban – ARISTOTLE (ongoing)
- AVERROES (ongoing)
- Rivaroxaban – ROCKETAF (ongoing)
  - Pending FDA approval for prophylaxis of DVT/PE in patients undergoing hip- or knee-replacement surgery (declined approval in May 2009 pending further evaluation)

Oral Anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Warfarin</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Vitamin K epoxide reductase</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Thrombin</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>40</td>
<td>3.2-5.1</td>
<td>8.15</td>
<td>7.1-17</td>
</tr>
<tr>
<td>Monitoring</td>
<td>INR-adjusted</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td>Administration</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Once- to twice daily</td>
<td>Once- to twice daily</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP450</td>
<td>66% fecal; 33% renal</td>
<td>75% fecal; 25% renal</td>
<td>20% fecal; 80% renal</td>
</tr>
<tr>
<td>Antidote or treatment of bleeding</td>
<td>VKK + FFP, APC, or recombinant FVIIa</td>
<td>Recombinant Factor Xa derivative, APC, recombinant FVIIa</td>
<td>Recombinant Factor Xa derivative</td>
<td>No antidote</td>
</tr>
<tr>
<td>Assay</td>
<td>PT/INR</td>
<td>Anti-factor Xa, PCT, HEP test</td>
<td>Anti-factor Xa</td>
<td>Eucaryotic cell</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>CYP2C9, 1A2, 2C39</td>
<td>CYP 3A4 Inhibitor</td>
<td>CYP 3A4 Inhibitor</td>
<td>FPF decrease absorption</td>
</tr>
</tbody>
</table>

Pharmacist Run Anticoagulation Clinical Data

<table>
<thead>
<tr>
<th>Measure</th>
<th>Usual Care Model</th>
<th>Nurse Model</th>
<th>Pharmacist Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR time in range (%)*</td>
<td>57.4</td>
<td>71.8</td>
<td>83.6</td>
</tr>
<tr>
<td>INR values in range (%)/</td>
<td>49.4</td>
<td>67.3</td>
<td>74.9</td>
</tr>
<tr>
<td>INR + 5.0 (%)*</td>
<td>2.9</td>
<td>2.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate (#/100)†</td>
<td>13.9</td>
<td>12.3</td>
<td>5.4</td>
</tr>
<tr>
<td>Relative Risk (95% CI)†</td>
<td>2.59 (1.29-5.13)</td>
<td>2.29 (1.23-4.25)</td>
<td>---</td>
</tr>
<tr>
<td>ED visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate (#/100)†</td>
<td>5.6</td>
<td>5.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Relative Risk (95% CI)†</td>
<td>4.40 (1.24-15.99)</td>
<td>4.40 (1.42-13.98)</td>
<td>---</td>
</tr>
</tbody>
</table>

* p < 0.05 for all comparisons vs pharmacist
† p < 0.01 for all comparisons vs. pharmacist
Aspirin for Primary Prevention

- What does the trial data tell us?
- Is there a difference in men versus women?
- What are the consensus guideline recommendations?

Primary Prevention Trials

<table>
<thead>
<tr>
<th>BWC</th>
<th>PHS</th>
<th>TPT</th>
<th>HCT</th>
<th>PPP</th>
<th>WBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>19.8</td>
<td>19.8</td>
<td>19.8</td>
<td>19.8</td>
<td>19.8</td>
</tr>
<tr>
<td>Patients</td>
<td>1,250</td>
<td>1,000</td>
<td>750</td>
<td>1,000</td>
<td>1,000</td>
</tr>
<tr>
<td>Dosage</td>
<td>350 mg daily</td>
<td>250 mg daily</td>
<td>75 mg daily</td>
<td>100 mg daily</td>
<td>100 mg daily</td>
</tr>
</tbody>
</table>

Questions

What do you think this patients Framingham CHD Risk Score is?

What is this patients Framingham Stroke Risk Score?

Should this patient be taking aspirin daily?

FDA Rulings on Aspirin

- December 8, 2003
  - The FDA’s Cardiovascular and Renal Drug Advisory Committee votes not to approve aspirin for the primary prevention of myocardial infarction (MI).
  - The committee voted overwhelmingly against the petition sought by Bayer Corp
    - Petition: To approve ASA for the reduction of risk of a first MI in moderate risk patients, those with a 10 year CHD risk of < 20%,
    - Voting:
      - 11 against, 3 for approval
  - Despite the existing data (5 major trials at the time), the committee felt the evidence supporting the extended label for ASA was inconsistent at best or lacking at worst.

Vignette

HPI: TF is a 60 yof who is in clinic today for a yearly check up. She reports taking her medications as prescribed and tries to exercise most days of the week which is usually walking 30-45 minutes.

PMH: Hypertension
Dyslipidemia
Social Hx: (+) tobacco (1ppd x 35 years); (-) ETOH
Current medications include: All: NKDA
HCTZ 25 mg po daily
atorvastatin 10mg po qhs
lisinopril 5 mg po daily
Vitals/Labs today at ED are as follows:
BP 135/90, HR 80, RR 25, Ht 5’5”, Wt 140 lbs
TC 170, LDL-C 120, HDL-C 45, TG 130

What is this patients Framingham Stroke Risk Score?
Antithrombotic Trialists’ Collaboration

Meta-Analysis Aspirin for Primary Prevention (Men vs. Women)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage of Patients (Odds Ratio [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Events</td>
<td>Men: 4.41% vs. 4.63% (0.75 vs. 0.90)</td>
</tr>
<tr>
<td></td>
<td>Women: 2.35% vs. 2.66% (0.88 vs. 0.90)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>Men: 1.96% vs. 2.76% (0.88 vs. 1.01)</td>
</tr>
<tr>
<td></td>
<td>Women: 0.92% vs. 0.91% (0.91 vs. 1.01)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>Men: 1.00% vs. 1.61% (0.97 vs. 0.96)</td>
</tr>
<tr>
<td></td>
<td>Women: 0.84% vs. 1.06% (0.85 vs. 1.04)</td>
</tr>
<tr>
<td>CV Mortality</td>
<td>Men: 0.99% vs. 1.09% (0.86 vs. 0.90)</td>
</tr>
<tr>
<td></td>
<td>Women: 0.90% vs. 0.99% (0.94 vs. 1.00)</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>Men: 0.95% vs. 1.10% (0.95 vs. 1.10)</td>
</tr>
<tr>
<td></td>
<td>Women: 0.99% vs. 1.10% (0.94 vs. 1.00)</td>
</tr>
</tbody>
</table>

Benefits

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage of Patients (Odds Ratio [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major CHD</td>
<td>Men: 0.86% vs. 0.88% (0.74 vs. 0.88)</td>
</tr>
<tr>
<td></td>
<td>Women: 0.76% vs. 0.86% (0.63 vs. 0.93)</td>
</tr>
<tr>
<td>Non-Fatal MI</td>
<td>Men: 2.35% vs. 2.35% (1.00 vs. 1.00)</td>
</tr>
<tr>
<td></td>
<td>Women: 2.89% vs. 2.89% (0.93 vs. 0.94)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>Men: 0.84% vs. 0.84% (0.79 vs. 0.90)</td>
</tr>
<tr>
<td></td>
<td>Women: 0.76% vs. 0.84% (0.63 vs. 0.93)</td>
</tr>
<tr>
<td>CHD Mortality</td>
<td>Men: 0.99% vs. 0.99% (0.86 vs. 1.01)</td>
</tr>
<tr>
<td></td>
<td>Women: 0.90% vs. 0.90% (0.84 vs. 1.00)</td>
</tr>
</tbody>
</table>

Risks

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage of Patients (Odds Ratio [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>Men: 0.81% vs. 0.68% (0.48 vs. 1.00)</td>
</tr>
<tr>
<td></td>
<td>Women: 0.71% vs. 0.97% (0.46 vs. 1.68)</td>
</tr>
</tbody>
</table>

Consensus Guidelines

<table>
<thead>
<tr>
<th>Organization</th>
<th>Population</th>
<th>Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA (primary)</td>
<td>10-yr CHD Risk ≥ 10%</td>
<td>75-160</td>
</tr>
<tr>
<td>AHA (secondary)</td>
<td>All patients with contraindications</td>
<td>75-162</td>
</tr>
<tr>
<td>ADA (DM only)</td>
<td>10-yr CHD Risk ≥ 10% or Men &gt; 50 or women &gt; 65 with 1 major CV Risk Factor*</td>
<td>75-162</td>
</tr>
<tr>
<td></td>
<td>All patients with history of CVD</td>
<td>75-162</td>
</tr>
<tr>
<td>USPSTF</td>
<td>see table on next page</td>
<td>75-162.5</td>
</tr>
<tr>
<td>ACCP</td>
<td>10-yr CHD Risk ≥ 10%</td>
<td>75-100</td>
</tr>
<tr>
<td>ASHP</td>
<td>Possibly for 10-yr CHD Risk ≥ 6% or Yes for 10-yr CHD Risk ≥ 10%</td>
<td>75-162</td>
</tr>
</tbody>
</table>

*Major CV Risk Factors include: family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria

USPSTF Recommendations

<table>
<thead>
<tr>
<th>Risk Level at Which CVD Events Prevented Exceeds GI Harms</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 10 year CHD Risk</td>
<td>Age 10 year Stroke Risk</td>
<td></td>
</tr>
<tr>
<td>45-59 ≥ 4%</td>
<td>45-59 ≥ 3%</td>
<td></td>
</tr>
<tr>
<td>60-69 ≥ 8%</td>
<td>60-69 ≥ 8%</td>
<td></td>
</tr>
<tr>
<td>70-79 ≥ 11%</td>
<td>70-79 ≥ 11%</td>
<td></td>
</tr>
</tbody>
</table>

Primary Prevention Meta-analysis

<table>
<thead>
<tr>
<th>RR, serious vascular events (95% CI)</th>
<th>RR, extracranial bleeding (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATTC (6 trials)*</td>
<td>0.88 (0.82-0.94)</td>
</tr>
<tr>
<td>ATTC + JPAD, POPADAD, AAA</td>
<td>0.90 (0.85-0.96)</td>
</tr>
</tbody>
</table>

Recent Trials

- Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial
  - Low dose ASA as primary prevention did not reduce the risk of cardiovascular events in T2DM
- Prevention and Progression of Arterial Disease and Diabetes (POPADAD)
  - Low dose ASA no CV event benefit as primary prevention in patients with asymptomatic PAD and Diabetes
- Aspirin for Asymptomatic Atherosclerosis (AAA) trial
  - Low dose ASA no reduction in vascular events in asymptomatic subjects with a low ankle/brachial index (ABI)
Clopidogrel/PPI Interaction

- Does a drug interaction exist?
- What about pharmacogenomic issues?
- What has the data shown us?
- How do we manage in the outpatient setting?

Vignette

HPI: TF is a 70 yof who is presenting to clinic for a follow-up visit to get her INR checked. She is frustrated by needing to come into clinic every 2-3 weeks since last being hospitalized 3 months ago to have her INR checked. She wants to go off of the warfarin because of the monitoring.

PMH: STEMI (2 stents placed 3 month ago)
- Atrial Fibrillation (chronic)
- Hypertension
- Dyslipidemia
- Social Hx: (-) tobacco; (-) ETOH

Vignette

Current medications include: All: NKDA
- metoprolol tartrate 50 mg po bid
- warfarin 5mg MWF, 7.5 mg all other days
- simvastatin 40mg po qhs
- lisinopril 20 mg po daily
- aspirin 81 mg po daily
- clopidogrel 75 mg po daily

Vitals/Labs today at clinic are as follows:
BP 130/85, HR 70, RR 25, Ht 5’7”, Wt 150 lbs
INR = 2.2

Questions

Should this patient be on a proton pump inhibitor? Are specific PPIs preferred?

Is an H2 Blocker an option for this patient?

Algorithm Assessing the Need for PPI

Drug Interaction

- Clopidogrel is a prodrug and must be metabolized by the cytochrome P450 isoenzymes CYP3A5 and CYP2C19 to active metabolites
- PPIs can competitively inhibit CYP2C19
  - Most Potent: Lansoprazole
  - Least Potent: Rabeprazole (parent compound)

- Reduction of active metabolites can decrease the antiplatelet effect of clopidogrel
- The antiplatelet effect of clopidogrel can be affected by polymorphisms in CYP2C19

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Page 5 of 8
**New FDA Boxed Warning**

Warn about reduced effectiveness in patients who are poor metabolizers of clopidogrel. Poor metabolizers do not effectively convert clopidogrel to its active form in the body.

Inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.

Advise healthcare professionals to consider use of other anti-platelet medications or alternative dosing strategies for clopidogrel in patients identified as poor metabolizers.


---

**CYP2C19 Genotype Frequencies by Race**

- **Caucasian**
  - 100%
- **African-American**
  - 100%
- **Asian**
  - 100%

---

**OCLA**

- **Treatment Arms:**
  - Omeprazole 20 mg daily
  - Placebo
- **Eligible patients:**
  - Elective PCI w/Stent
- **Exclusion Criteria:**
  - Previous Tx clopidogrel
  - Previous Tx PPI
  - Hx of thrombocytopenia
  - Liver disease
  - Hx GI ulcer
- **Primary Endpoint (7 days):**
  - Platelet Reactivity Index (PRI)

---

**Risk of Adverse Outcomes Associated With Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Acute Coronary Syndrome**

Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, Rumsfeld JS

JAMA 2009;301:937-44.

---

**Adverse Outcomes Following Hospitalization for ACS**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopidogrel without PPI (N=2961)</th>
<th>Clopidogrel with PPI (N=2544)</th>
<th>OR (95%CI)</th>
<th>Adj OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or rehospitalization for ACS</td>
<td>20.8</td>
<td>29.8</td>
<td>1.62 (1.45-1.80)</td>
<td>1.25 (1.11-1.44)</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat revascularization for ACS</td>
<td>6.9</td>
<td>14.8</td>
<td>2.29 (1.95-2.69)</td>
<td>1.88 (1.57-2.20)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>11.9</td>
<td>15.5</td>
<td>1.38 (1.19-1.55)</td>
<td>1.49 (1.30-1.71)</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>16.8</td>
<td>19.9</td>
<td>1.24 (1.10-1.40)</td>
<td>0.91 (0.80-1.05)</td>
</tr>
</tbody>
</table>

ACS = Acute Coronary Syndrome; PPI = proton pump inhibitor; OR = odds ratio

JAMA 2009;301:937-44.
A population-based study of the drug interaction between proton pump inhibitors and clopidogrel

Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, Henry DA, Kopp A, Mamdani MM

CMAJ. 2009;180:713-8.

Association between PPI and Adverse Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cases (n/N)</th>
<th>Controls (n/N)</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent MI &lt; 90 days</td>
<td>194/734</td>
<td>426/2057</td>
<td>1.27 (1.03-1.57)</td>
</tr>
<tr>
<td>Previous Recurrent MI</td>
<td>63/734</td>
<td>195/2057</td>
<td>0.86 (0.63-1.19)</td>
</tr>
<tr>
<td>Remote Recurrent MI</td>
<td>17/734</td>
<td>68/2057</td>
<td>0.81 (0.48-1.41)</td>
</tr>
<tr>
<td>Death &lt; 90 days</td>
<td>71/323</td>
<td>188/916</td>
<td>0.82 (0.57-1.21)</td>
</tr>
</tbody>
</table>

Proton Pump Inhibitor

<table>
<thead>
<tr>
<th>PPI</th>
<th>Cases (n/N)</th>
<th>Controls (n/N)</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoprazole</td>
<td>46/734</td>
<td>125/2057</td>
<td>1.02 (0.70-1.47)</td>
</tr>
<tr>
<td>Other</td>
<td>148/734</td>
<td>259/2057</td>
<td>1.40 (1.10-1.77)</td>
</tr>
<tr>
<td>H2 Blocking agent</td>
<td>37/734</td>
<td>106/2057</td>
<td>0.94 (0.63-1.40)</td>
</tr>
</tbody>
</table>

Society of Cardiovascular Angiography and Interventions (SCAI) Statement

“SCAI urges health care providers who are treating post-stenting patients on dual-antiplatelet therapy to consider prescribing a histaminergic (H2) blocker or antacids instead of a PPI considering the high risk for adverse events shown in this study. H2 blockers are not metabolized by the CYP enzyme system that is responsible for activating the pro-drug, clopidogrel, into the active metabolite of clopidogrel that has antiplatelet actions. Therefore, there is no inhibition of the antiplatelet effect of clopidogrel by H2 blockers.”


TRITON-TIMI-38

CLOPIDOGREL PPI vs no PPI: Adj HR 0.94, 95% CI 0.80-1.11
PRASUGREL PPI vs no PPI: Adj HR 1.00, 95% CI 0.84-1.20

2010 Summer Meeting Supplemental Handout
Take Home Message

• Refer to CHEST guidelines to determine who is indicated for Anticoagulation in patients with Atrial Fibrillation.

• New oral anticoagulation agents are currently being studied in the Atrial Fibrillation population and may be FDA approved in the future.

Take Home Message

• 2009 USPSTF guidelines for primary prevention of cardiovascular disease with ASA indicate therapy based on risk.

• Controversy remains about what CHD or Stroke Risk indicates ASA in a primary prevention population.

Take Home Message

• A drug interaction between PPIs and clopidogrel exists, but the clinical implications are variable based on patient populations.

• Focus should be placed on evaluating whether a patient needs GI protection with a PPI or H2 Blocker while receiving dual antiplatelet therapy.