Oral Antiplatelet Therapies and the Treatment of Atherothrombosis: A Practical Guide for the Pharmacy Provider

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PharmCon is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

1. Confidently assess and counsel patients regarding their modifiable risk factors in the prevention of an atherosclerotic event
2. Increase patient counseling discussions regarding the importance of antiplatelet therapy adherence to prevent atherosclerotic events
3. Discuss various treatment options for peripheral arterial disease (PAD), and when it is beneficial to use antiplatelet therapy
4. Identify appropriate patient scenarios for antiplatelet therapy use in primary and secondary interventions
Atherothrombosis Is a Leading Cause of Mortality

AIDS: acquired immune deficiency syndrome

REACH Registry: High Prevalence of Risk Factors for Atherothrombosis

CAD: 37.0%
CVD: 26.0%
PAD: 3.6%
Risk factors only: 20.4%

Coronary artery disease (CAD): Stable or unstable angina, myocardial infarction, angioplasty/stenting, coronary artery bypass graft (CABG)
Cardiovascular disease (CVD): TIA, stroke
PAD: History or current intermittent claudication with ankle brachial index < 0.9, angioplasty/stenting, or amputation
Risk factors only: at least 3 risk factors with no symptomatic atherothrombosis

REACH: Reduction of Atherothrombosis for Continued Health
REACH: Atherothrombosis Has Both Fatal and Nonfatal Outcomes

Number at Risk

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death, MI, stroke</td>
<td>0 1 2 3 4 5 6</td>
</tr>
<tr>
<td>CV Death</td>
<td>64,692 64,296</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>64,749 64,555</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>64,723 64,471</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>0 1 2 3 4 5 6 7 8 9 10 11 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>63,642 63,029 62,702 62,576</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>64,045 62,702 61,122 60,910</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>63,979 62,576 51,360 23,889</td>
</tr>
</tbody>
</table>

CV: cardiovascular
MI: myocardial infarction

Atherothrombosis Also Leads to Death From Peripheral Vascular Disease

Kaplan-Meier survival curves based on mortality from all causes

- Normal subjects (n = 408)
- Asymptomatic LV-PAD (n = 49)
- Symptomatic LV-PAD (n = 18)
- Severe LV-PAD (n = 13)

LV-PAD: large-vessel PAD

Roles of Various Risk Factors in the Development of Vascular Disease

Primary Metabolic Disturbance → Intermediate Vascular Disease Risk Factor → Intravascular Pathology → Clinical Event

- Overnutrition
  - Insulin Resistance
  - Hypertension
  - Dyslipidemia
  - Hyperglycemia
  - Hyperinsulinemia
  - Inflammation
  - Impaired Fibrinolysis
  - Endothelial Dysfunction

Atherosclerosis:
- Coronary arteries
- Carotid arteries
- Cerebral arteries
- Aorta
- Peripheral arteries

Hypercoagulability

Atheroma Development

Adapted from: Pepine CJ. Am J Cardiol. 1998;82(10A):23S-27S.

Foam cells | Fatty streak | Intermediate lesion | Atheroma | Complicated lesion/rupture | Fibrous plaque

Endothelial Dysfunction

From first decade | From third decade | From fourth decade

Growth mainly by lipid accumulation | Thrombosis hematoma | Accelerated smooth muscle and collagen increase

Adapted from: Pepine CJ. Am J Cardiol. 1998;82(10A):23S-27S.
Factors Contributing to Platelet Activation and Thrombus Formation

- Injury
  - Adhesion
    - vWF
    - Thrombin
    - Collagen
    - Fibronectin
  - Shear Forces
    - vWF
    - ADP receptor
  - Activation
    - Membrane changes
    - Granule secretion
    - Glycoprotein (GP) IIb/IIIa expression
    - Multiple agonists
    - Feedback loops
  - Aggregation
    - vWF
    - GP IIb/IIIa-mediated
    - Fibrinogen

ADP: adenosine diphosphate
vWF: von Willebrand factor

Case Study

Evan is a 68-year-old male presenting for his annual physical examination with his primary care practitioner. He has a past medical history significant for hypertension, hyperlipidemia, and a 40 pack-year smoking history. He describes a fairly sedentary lifestyle. He is attempting to stop smoking and has just recently begun using a nicotine patch. Evan claims he is very compliant with his medications.

- BMI, 31.3 kg/m$^2$ (5’ 8”, 206 lbs)
- Blood pressure, 145/79 mm Hg
- LDL-cholesterol, 126 mg/dL

Medications
- Lisinopril (10 mg daily)
- Hydrochlorothiazide (25 mg daily)
- Simvastatin (20 mg daily).
Case Study Question

Based on Evan’s presenting risk factors, what is his 10-year risk of developing a significant cardiovascular event?

A. No risk (< 1%)
B. Low risk (< 3%)
C. Intermediate risk (> 10%)
D. High risk (> 20%)
### INTERHEART Trial: Nine Risk Factors Account for 90% of Myocardial Infarctions

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>PAR (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoB/ApoA-1</td>
<td>3.25</td>
<td>49.2%</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>2.04</td>
<td>35.7%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.37</td>
<td>9.9%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.91</td>
<td>17.9%</td>
</tr>
<tr>
<td>Abdominal Obesity</td>
<td>1.62</td>
<td>20.1%</td>
</tr>
<tr>
<td>Psychosocial Factors</td>
<td>2.67</td>
<td>32.5%</td>
</tr>
<tr>
<td>Daily Consumption of Fruits and Vegetables</td>
<td>0.70</td>
<td>13.7%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.91</td>
<td>6.7%</td>
</tr>
<tr>
<td>Regular Exercise</td>
<td>0.86</td>
<td>12.2%</td>
</tr>
</tbody>
</table>

9 risk factors accounted for 90% of the PAR in men and 94% in women

Screening Asymptomatic Patients by Noninvasive Testing

Risk Calculators*

Low Risk

Intermediate Risk
(> 10% at 10 years for CV event)

High Risk
(> 20% at 10 years)

Weight Loss Is the Most Important
Healthy diet
Exercise

Noninvasive Testing
(EET, nuclear, stress echo, 64 slice computed tomography, others)

High Risk Early Positive Cardiology Consult

* Framingham Heart Study (nondiabetes):
United Kingdom Prospective Diabetes Study (Diabetes):
  http://www.dtu.ox.ac.uk/riskengine
Reynolds Score (women):
  http://www.reynoldsriskscore.org
# NCEP-ATP III: Therapeutic Lifestyle Changes to Reduce Cardiovascular Risk

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate TLC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk</strong>: coronary heart disease (CHD) or CHD equivalent (10-year risk &gt; 20%)</td>
<td>&lt; 100 mg/dL (or &lt; 70 mg/dL)</td>
<td>≥ 100 mg/dL</td>
</tr>
<tr>
<td><strong>Moderately High Risk</strong>: 2+ risk factors (10-year risk: 10%-20%)</td>
<td>&lt; 130 mg/dL</td>
<td>≥ 130 mg/dL</td>
</tr>
<tr>
<td><strong>Moderate Risk</strong>: 2+ risk factors (10-year risk &lt; 10%)</td>
<td>&lt; 130 mg/dL</td>
<td>≥ 130 mg/dL</td>
</tr>
<tr>
<td><strong>Lower Risk</strong>: 0-1 risk factor(s)</td>
<td>&lt; 160 mg/dL</td>
<td>≥ 160 mg/dL</td>
</tr>
</tbody>
</table>

*Therapeutic lifestyle changes (TLCs) are still essential to cholesterol management.*

NCEP-ATP III: National Cholesterol Education Program Adult Treatment Panel III

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong>: CHD or CHD equivalent</td>
<td>&lt; 100 mg/dL (or &lt; 70 mg/dL)</td>
<td>≥ 100 mg/dL (&lt; 100 mg/dL; consider drug options)</td>
</tr>
<tr>
<td>(10-year risk &gt; 20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderately high risk</strong>: 2+ risk factors</td>
<td>&lt; 130 mg/dL</td>
<td>≥ 130 mg/dL (100-129 mg/dL; consider drug options)</td>
</tr>
<tr>
<td>(10-year risk: 10%-20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate risk</strong>: 2+ risk factors</td>
<td>&lt; 130 mg/dL</td>
<td>≥ 160 mg/dL</td>
</tr>
<tr>
<td>(10-year risk &lt; 10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lower risk</strong>: 0-1 risk factor(s)</td>
<td>&lt; 160 mg/dL</td>
<td>≥ 190 mg/dL (160-189 mg/dL; LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>

- A high-risk patient with high triglycerides or low high-density lipoprotein–cholesterol (HDL-C), should consider combining LDL-lowering therapy with fibrate or nicotinic acid
- LDL-lowering therapy in a high-risk or moderately high-risk patient should reduce LDL-C by 30%-40%

## CHS: Independent Risk Factors for Low (< 0.9) Ankle-Arm Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR*</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (5 year)</td>
<td>1.69</td>
<td>(1.50-1.92)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Race (nonwhite)</td>
<td>2.12</td>
<td>(1.31-3.44)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total Cholesterol (10 mg/dL)</td>
<td>1.10</td>
<td>(1.06-1.14)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HDL-C (1 mg/dL)</td>
<td>0.99</td>
<td>(0.98-1.00)</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine (0.1 mg/dL)</td>
<td>1.07</td>
<td>(1.13-1.12)</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.94</td>
<td>(0.91-0.97)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Forced Vital Capacity (L)</td>
<td>0.63</td>
<td>(0.52-0.76)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Reported Diabetes</td>
<td>4.05</td>
<td>(2.79-5.90)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>2.55</td>
<td>(1.76-3.68)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Pack Years</td>
<td>1.01</td>
<td>(1.01-1.02)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Reported Hypertension</td>
<td>1.51</td>
<td>(1.15-1.99)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

* Relative risk of ankle-arm index < 0.9 determined by stepwise multiple logistic regression

(n = 5084)

Aspirin Resistance Leads to Ischemic Events Despite Receiving Aspirin

**Cellular Factors:**
- Insufficient suppression of cyclooxygenase (COX)-1
- Overexpression of COX-2 messenger ribonucleic acid
- Increased norepinephrine
- Generation of 8-iso-PGF$_{2\alpha}$

**Clinical Factors:**
- Failure to prescribe
- Noncompliance
- Nonabsorption
- Interaction with ibuprofen

**Genetic Polymorphisms:**
- COX-1
- GP IIa receptor
- Collagen receptor
- vWF receptor

Oral Antiplatelet Agents

- Thromboxane A$_2$ (TXA$_2$) inhibitor:
  - Acetylsalicylic acid (ASA)
- Phosphodiesterase inhibitor:
  - Dipyridamole
  - Cilostazol
- ADP-receptor antagonists:
  - Clopidogrel
  - Ticlopidine
Oral Antiplatelet Agents: Mechanisms of Action

Platelet Activation

- Aspirin
- Thromboxane A₂ receptor
- COX2
- TXA₂
- Intracellular Ca²⁺ mobilization
- ADP receptor (clopidogrel)
- ADP phosphodiesterase (dipyridamole)
- cAMP phosphodiesterase (dipyridamole)
- cAMP
- ADP
- TXA₂
- Aspirin
Stroke and Oral Antiplatelet Therapy

- Each year in the United States:
  - Over 700,000 strokes, resulting in 150,000 deaths
  - 180,000 of these patients with second stroke
  - 500,000 TIAs
- Resulting in 4.7 million stroke survivors
  - 90% of which will have deficits
  - Leading cause of long-term disability among adult patients

Poststroke Mortality

- Approximately 50% of poststroke victims will die within 5 years:
  - TIA: 50%
  - Acute ischemic stroke: approximately 60%

- Most likely causes of death:
  - Cardiovascular (acute myocardial infarction [AMI])
  - Cerebrovascular (stroke)

Bhatt DL. *Am J Cardiol*. 2006;98(12A):22Q-29Q.
Aspirin and Secondary Stroke Prevention

- Aspirin has been shown to reduce the risk of recurrent stroke by 20%-25%
- Recommended dose: 50-325 mg daily\(^1\)
- Evidence has suggested that potentially 30% of the patients on low-dose aspirin for secondary stroke prevention may be “resistant” to lower doses and require higher doses or alternative antiplatelet therapy\(^2\)
- The addition of aspirin to clopidogrel may increase the risk of bleeding and is not routinely recommended for stroke or TIA patients unless they have a specific indication for this therapy (ie, ACS or coronary stent)\(^1\)

---


## Risk of Stroke Increases Dramatically With Atherothrombosis

<table>
<thead>
<tr>
<th>Preceding Event</th>
<th>AMI</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>5 to 7 fold (includes death)</td>
<td>3 to 4 fold (includes TIA)</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2 to 3 fold (includes angina and sudden death)</td>
<td>9 fold</td>
</tr>
<tr>
<td>Peripheral Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>4 fold (includes fatal myocardial infarction and other CHD death)</td>
<td>2 to 3 fold (includes TIA)</td>
</tr>
</tbody>
</table>

---

CAPRIE: Reduced Risk of Myocardial Infarction, Ischemic Stroke, or Vascular Death

- Subjects had recent myocardial infarction, recent ischemic stroke, or established PAD
- Median follow-up: 1.91 years (n = 19,185)

No significant between-group difference for reports of any bleeding disorder (clopidogrel: 9.27%; aspirin: 9.28%)

ESP2S: Stroke Prevention With Combined Aspirin and Dipyridamole


2-year incidence of stroke

Risk Reduction (%)

- ASA
- Dipyridamole
- ASA+Dipyridamole

Risk Reduction (%)

$p = 0.013$  $p = 0.039$  $p < 0.001$
MATCH: No Reduction in Primary End Point With Addition of Aspirin

Primary end point: first occurrence of ischemic stroke, myocardial infarction, vascular death, or rehospitalization for an acute ischemic event

MATCH: Management of Atherothrombosis With Clopidogrel in High-Risk Patients

Number at Risk
Aspirin plus clopidogrel 3797 3576 3440 3321 3229 3130 2441
Placebo plus clopidogrel 3802 3576 3439 3326 3200 3119 2446

Risk of life-threatening (1.3%) or major bleeding (1.4%) was significantly increased ($P < 0.0001$) following addition of aspirin.

ESPRIT: Aspirin Plus Dipyridamole Reduces Primary Outcome

ESPRIT: European/Australasian Stroke Prevention in Reversible Ischaemia Trial

- A lower rate of major complications with dipyridamole was not significant
- Rates of minor bleeding complications were equal between the 2 groups

* Composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction or major bleeding complication

PRoFESS: Comparison of Antiplatelet Regimens in Stroke Recurrence

Cumulative probability of recurrent stroke

- Clopidogrel (8.8% recurrence)
- Aspirin plus ERDP (9.0% recurrence)

Years since randomization

HR 1.01 (95% CI, 0.92-1.11)

Minor or Major Hemorrhagic Events
- Aspirin plus ERDP: 535 (5.3%)
- Clopidogrel: 494 (4.9%)
- HR (95% CI): 1.08 (0.96-1.22)

AHA/ASA Recommendations for Antiplatelet Therapy

**Class I Recommendations**

**Recommendation**: For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events (*Class I, Level of Evidence A*).

**New recommendation**: Aspirin (50-325 mg/day) monotherapy, the combination of aspirin and ERDP, and clopidogrel monotherapy are all acceptable options for initial therapy (*Class I, Level of Evidence A*).*

**New recommendation**: The combination of aspirin and ERDP is recommended over aspirin alone (*Class I, Level of Evidence B*).

* For patients who have an ischemic cerebrovascular event while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered for noncardioembolic patients, no single agent or combination has been well-studied in patients who have had an event while receiving aspirin.

AHA/ASA Recommendations for Antiplatelet Therapy

Class II Recommendations

Clopidogrel may be considered over aspirin alone on the basis of direct comparison trials (Class IIb, Level of Evidence B).

For patients allergic to aspirin, clopidogrel is reasonable (Class IIa, Level of Evidence B).

Class III Recommendation

The addition of aspirin to clopidogrel increases the risk of hemorrhage. Combination therapy of aspirin and clopidogrel is not routinely recommended for ischemic stroke or TIA patients unless they have a specific indication for this therapy (ie, coronary stent or ACS) (I).

Stroke Summary

• Stroke is the third leading cause of death, the first leading cause of long-term disability, and has been shown to significantly increase the risk of AMI, PAD, and a second stroke

• Pharmacists can play a pivotal role in stroke primary prevention by addressing risk factors (ie, smoking, hypertension, hyperlipidemia, and diabetes)

• Oral antiplatelet therapy is the cornerstone to optimizing secondary stroke prevention

http://www.cdc.gov/Stroke/index.htm
ACS and Oral Antiplatelet Therapy

- Estimates for the U.S. in 2008:
  - New ACS: 770,000 patients
  - Recurrent attack: 430,000 patients
  - About 38% of the patients who present with ACS in a given year will die from it

- The use of oral antiplatelet agents in ACS continues to evolve rapidly:
  - Timing of clopidogrel dosing with relation to PCI
  - Loading dose of clopidogrel
  - Duration of pharmacotherapy
  - Bleeding risk

## Oral Antiplatelet Trials in ACS Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>Clopidogrel*</th>
<th>Clopidogrel vs Placebo</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Primary Outcome</td>
<td>n</td>
<td>Primary Outcome</td>
</tr>
<tr>
<td>CURE¹</td>
<td>6303</td>
<td>11.4%</td>
<td>6259</td>
<td>9.3%</td>
</tr>
<tr>
<td>PCI-CURE²</td>
<td>1345</td>
<td>7.2%</td>
<td>1313</td>
<td>4.2%</td>
</tr>
<tr>
<td>CREDO³</td>
<td>1063</td>
<td>11.5%</td>
<td>1053</td>
<td>8.5%</td>
</tr>
<tr>
<td>PCI-CLARITY⁴</td>
<td>930</td>
<td>6.2%</td>
<td>933</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

* 300-mg loading dose followed by 75 mg daily in addition to daily aspirin

CLARITY: Clopidogrel Reduces Risk of Cardiovascular Death Before or After PCI

**PCI-CURE**
- **Odds Ratio (95% CI):** 0.70 (0.48-1.02)

**CREDO**
- **Odds Ratio (95% CI):**...

**PCI-CLARITY**
- **Odds Ratio (95% CI):** 0.63 (0.41-0.97)

**Overall**
- **Odds Ratio (95% CI):** 0.67 (0.50-0.89)

**Risk of myocardial infarction before PCI**
- **Odds Ratio (95% CI):** 0.65 (0.43-0.98)
- **Odds Ratio (95% CI):** 0.83 (0.57-1.21)
- **Odds Ratio (95% CI):** 0.60 (0.38-0.96)
- **Odds Ratio (95% CI):** 0.71 (0.56-0.89)

**Risk of cardiovascular death or myocardial infarction after PCI to 30 days**
- **Odds Ratio (95% CI):** 0.60 (0.38-0.96)
- **Odds Ratio (95% CI):** 0.71 (0.56-0.89)

*P = 0.005*

*P = 0.004*

Triton-TIMI: Prasugrel Significantly Reduces Ischemic Events

Increased risk of major bleeding was associated with prasugrel


**Primary End Point**
HR 0.81 (95% CI, 0.73-0.90)
P < 0.001

**Key Safety End Point**
HR 1.32 (95% CI, 1.03-1.68)
P = 0.03
Meta-Analysis: Evidence Favoring Loading Doses > 300 mg

<table>
<thead>
<tr>
<th>Randomized Trials</th>
<th>(n/N) High Loading</th>
<th>(n/N) Standard Loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALBION (2006)</td>
<td>2/68</td>
<td>1/35</td>
</tr>
<tr>
<td>CLEAR PLATELETS (2005)</td>
<td>1/60</td>
<td>3/60</td>
</tr>
<tr>
<td>Cuisset, et al. (2006)</td>
<td>7/146</td>
<td>15/146</td>
</tr>
<tr>
<td>Gurbel, et al. (2005)</td>
<td>0/52</td>
<td>0/138</td>
</tr>
<tr>
<td>ISAR-CHOICE (2005)</td>
<td>0/40</td>
<td>0/20</td>
</tr>
<tr>
<td>Muller, et al. (2001)</td>
<td>0/10</td>
<td>0/10</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>502</strong></td>
<td><strong>538</strong></td>
</tr>
</tbody>
</table>

Total events: 15 (high loading); 34 (standard loading)

Test for heterogeneity: \( \chi^2 = 0.75; \) df = 3 (\( P = 0.86 \)); \( I^2 = 0\% \)

Test for overall effect: \( Z = 2.93 \) (\( P = 0.003 \))

Studies reporting cardiac death or myocardial infarction within 1 month in patients receiving high versus standard loading doses

Meta-Analysis: Evidence Favoring Loading Doses > 300 mg

<table>
<thead>
<tr>
<th>Nonrandomized Trials</th>
<th>High Loading (n/N)</th>
<th>Standard Loading (n/N)</th>
<th>Total: All Studies (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiolillo, et al. (2004)</td>
<td>0/23</td>
<td>0/27</td>
<td>855</td>
</tr>
<tr>
<td>Seyfarth, et al. (2002)</td>
<td>0/11</td>
<td>0/21</td>
<td>712</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>353</strong></td>
<td><strong>174</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>28 (high loading)</strong></td>
<td><strong>38 (standard loading)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 3.94; df = 4 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)

Studies reporting cardiac death or myocardial infarction within 1 month in patients receiving high versus standard loading doses

Class I* Recommendations

Start aspirin 75-162 mg daily and continue indefinitely in all patients unless contraindicated (Class I, level A†):

- For patients undergoing CABG, start aspirin within 48 hours after surgery to reduce saphenous vein graft closure. 100-325 mg daily dosing appears to be efficacious. Doses above 162 mg daily can be continued for up to 1 year (Class I, level B‡)

* Class I: conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective
† Level A: data derived from multiple randomized clinical trials or meta-analyses
‡ Level B: data derived from a single randomized trial or nonrandomized studies

AHA/ACC 2006 Guidelines for Antiplatelet Agents (Continued)

Class I Recommendations

Start and continue clopidogrel 75 mg daily in combination with aspirin for up to 12 months in patients after ACS or PCI with stent placement (≥ 1 month for bare metal stent, ≥ 3 months for sirolimus-eluting stent, ≥ 6 months for paclitaxel-eluting stent (Class I, level B):

- For patients undergoing PCI with stent placement, use aspirin 325 mg daily for 1 month for bare metal stent, for 3 months with sirolimus-eluting stents, and for 6 months with paclitaxel-eluting stents (Class I, level B)

Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely (Class I, level B)

ACS Summary

• ACS remains a leading cause of morbidity and mortality in the United States

• Use of oral antiplatelet agents in the contemporary management of ACS patients has proven to significantly improve outcomes and continues to evolve:
  – Aspirin remains the cornerstone of oral antiplatelet pharmacotherapy in ACS patients
  – Clopidogrel plays a crucial role in coronary stenting, especially in reducing stent thrombosis rates
  – Future considerations and study to include a greater understanding of ASA “resistance” and appropriate loading doses of clopidogrel in PCI
PAD and Oral Antiplatelet Therapy

• Approximately 8 million patients in the United States have PAD:
  – 12%-20% of Americans aged ≥ 65 years
  – Approximately only 25% are undergoing treatment
  – Considered an NCEP CHD risk equivalent
• Common risk factors for developing PAD:
  – Diabetes: 4 times greater risk
  – Smoking: 2.55 times greater risk
  – Hypertension: 1.5 times greater risk
  – Total cholesterol (10 mg/dL): 1.1 times greater risk

Annual mortality was higher in patients with PAD than in patients with myocardial infarction.
Guidance for the Pharmacist in Identifying Patients at High Risk for PAD

- Aged < 50 years with diabetes and 1 other risk factor:
  - Smoking
  - Hyperlipidemia
  - Hypertension
  - Hyperhomocysteinemia
- Aged 50-69 years with a history of smoking or diabetes
- Aged ≥ 70 years old
- Diagnosed with atherosclerotic coronary, renal, or carotid artery disease
- Leg symptoms upon exertion that are suggestive of claudication, or pain at rest
- Abnormal lower extremity pulses

CAPRIE: Reduction of Vascular Events With Clopidogrel or Aspirin

RR Reduction (%) (95% CI)
-40 -30 -20 -10 0 10 20 30 40

- Stroke
- Myocardial infarction
- PAD
- All patients

Aspirin better
Clopidogrel better

CHARISMA: Dual Therapy With Aspirin and Clopidogrel

Risk of Cardiovascular Death/Myocardial Infarction/Stroke

<table>
<thead>
<tr>
<th>Prior Event</th>
<th>Placebo</th>
<th>Clopidogrel</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Myocardial Infarction</td>
<td>8.3%</td>
<td>6.6%</td>
<td>0.774</td>
<td>0.031</td>
</tr>
<tr>
<td>Prior Ischemic Stroke</td>
<td>10.7%</td>
<td>8.4%</td>
<td>0.780</td>
<td>0.029</td>
</tr>
<tr>
<td>Prior PAD</td>
<td>8.7%</td>
<td>7.6%</td>
<td>0.869</td>
<td>0.285</td>
</tr>
<tr>
<td>Entire Cohort</td>
<td>8.8%</td>
<td>7.3%</td>
<td>0.829</td>
<td>0.010</td>
</tr>
</tbody>
</table>

CHARISMA: Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance

Improved Walking Distance in Patients With Intermittent Claudication

Maximal walking distance: mean change from baseline (%)

- Cilostazol 100 mg BID
- Pentoxifylline 400 mg TID
- Placebo

* $P < 0.05$ at all time points

2008 ACCP Guidelines for Oral Antiplatelet Therapies in PAD

- Aspirin is not recommended for prevention of venous thromboembolism in long-distance travel (Grade 1B):
  - *Avoid constrictive clothing, maintain adequate hydration, and exercise frequent calf-muscle contraction* (Grade 1C)
- For peripheral artery occlusive disease in patients with coronary or cerebrovascular disease, lifelong antiplatelet therapy is recommended (Grade 1A):
  - *If no clinically manifest coronary or cerebrovascular disease, aspirin (75-100 mg) is recommended over clopidogrel* (Grade 2B)
  - *If aspirin intolerant, clopidogrel is recommended over ticlopidine* (Grade 1B)

Grade 1: Strong recommendation (benefits do or do not outweigh risks, burdens, and costs)
Grade 2: Weaker recommendation (less certainty about magnitude of benefits and risks, burdens, and costs)
Quality of evidence: A: high, B: moderate, C: low

For routine prosthetic infrainguinal bypass, perioperative aspirin (75-100 mg) is recommended (Grade 1A).

For carotid endarterectomy, perioperative aspirin (75-100 mg) is recommended to prevent perioperative ischemic neurological events (Grade 1A):
- Lifelong postoperative aspirin (75-100 mg) is recommended (Grade 1A).

For asymptomatic carotid stenosis, lifelong aspirin (75-100 mg) is recommended (Grade 1C):
- Dual antiplatelet therapy with aspirin and clopidogrel is not recommended in this group (Grade 1B).

For lower-extremity balloon angioplasty (with or without stenting), long-term aspirin (75-100 mg) is recommended (Grade 1C).

PAD Summary

- PAD is a prevalent form of atherothrombosis
- The NCEP has classified PAD as a CHD risk equivalent
- Pharmacists can play a significant role in reducing cardiovascular events and death associated with PAD:
  - Increase provider and patient awareness of PAD
  - Reduce and treat risk factors associated with smoking, diabetes, hypertension, and dyslipidemia
  - Get patients to exercise
  - Provide antiplatelet therapy when appropriate
Putting It All Together: Appropriate Risk Reduction Strategies in Atherothrombosis

Comprehensive Risk Reduction Strategy

Reduce Vascular Risk
- Control hypertension
- Control diabetes
- Control cholesterol
- ASA or warfarin in atrial fibrillation

Reduce Behavioral Risk
- Stop smoking
- Decrease alcohol intake
- Lose weight
- Increase physical activity

Pharmacological
- Antiplatelet therapy:
  - ASA
  - Clopidogrel
Case Study Resolution

Briefly, remember Evan is a 68-year-old fairly healthy male. He has a past medical history significant for hypertension, hyperlipidemia, and a 40 pack-year smoking history. He does not exercise and is attempting to stop smoking with a nicotine patch. He has been compliant with his medications. His 10-year risk of developing a significant cardiovascular event was determined to be high (>20%).

Medications
- Lisinopril (10 mg daily)
- Hydrochlorothiazide (25 mg daily)
- Simvastatin (20 mg daily)

Plan:
- Smoking Cessation (on nicotine patch)
- Diet and exercise (3 to 5 times/week)
- Hypertension not controlled, increase lisinopril to 20mg daily

• BMI, 31.3 kg/m2 (5’ 8”, 206 lbs)
• Blood pressure, 145/79 mm Hg
• LDL-cholesterol, 126 mg/dL
### Lifestyle Changes Effectively Decrease Platelet Activation

<table>
<thead>
<tr>
<th>Thrombogenic Markers</th>
<th>Physical Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regular</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>↓</td>
</tr>
<tr>
<td>Factor VII</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma Viscosity</td>
<td>↓</td>
</tr>
<tr>
<td>Tissue Plasminogen Activator</td>
<td>↑</td>
</tr>
<tr>
<td>Plasminogen Activator 1</td>
<td>↓</td>
</tr>
<tr>
<td>Platelet Activation</td>
<td>↓</td>
</tr>
<tr>
<td>Fibrinopeptide A</td>
<td>Unknown</td>
</tr>
<tr>
<td>Thrombin Generation*</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

* A rise in thrombin generation is indicated by elevated levels of thrombin–antithrombin III complex and prothrombin fragments 1 + 2.
† In healthy subjects

Program Summary

• Atherothrombosis is a significant health care problem and remains the leading cause of increased morbidity and mortality in the United States.

• Pharmacists can play a significant role in the management of patients with atherothrombosis with risk reduction strategies and optimization of pharmacotherapy to achieve evidence-based goals.

• The use of oral antiplatelet agents has been proven to play an important role in the secondary prevention of atherothrombotic events in stroke, ACS, and PAD.