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

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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


Limitations in the measurement of mortality (%)

Athero-thrombosis Cancer Injury Pulmonary disease AIDS Infectious disease

AIDS: acquired immune deficiency syndrome

**REACH Registry: High Prevalence of Risk Factors for Atherothrombosis**

- 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: Atherothrombosis Has Both Fatal and Nonfatal Outcomes**

- CV death, MI, stroke
- Nonfatal MI
- Nonfatal stroke

**Atherothrombosis Also Leads to Death From Peripheral Vascular Disease**

- LV-PAD: large-vessel PAD

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**Cardiovascular disease (CVD):**
- TIA, stroke

**Risk factors only: 20.4% CAD 37.0% CVD 26.0%**
- PAD: 8.4% 0.9% 1.1% 2.5%

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**Event rate (%):**

- CV death, MI, stroke
- CV death
- Nonfatal MI
- Nonfatal stroke

**1-year cardiovascular event rates:**

- CV death, MI, stroke: 4.5, 4.0, 3.5, 3.0, 2.5, 2.0, 1.5, 1.0, 0.5
- CV death: 0
- Nonfatal MI: 0
- Nonfatal stroke: 0

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**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)
Roles of Various Risk Factors in the Development of Vascular Disease

Overnutrition

- Hyperinsulinemia
- Hyperglycemia
- Hypertriglyceridemia
- Hypertension
- Dyslipidemia
- Inflammation
- Impaired Fibrinolysis
- Endothelial Dysfunction

CVD

Intravascular Pathology

Primary Metabolic Disturbance

Intermediate Vascular Disease Risk Factor

Clinical Event

Factors Contributing to Platelet Activation and Thrombus Formation

- vWF
- Thrombin
- Collagen
- Fibrinogen
- GP IIb/IIIa

ADP: adenosine diphosphate
vWF: von Willebrand factor

From first decade: Foam cells, Fatty streak, Endothelial Dysfunction
From third decade: Foam cells, Fatty streak, Atheroma Development
From fourth decade: Complicated atheroma, Rupture, Thrombus

Growth mainly by lipid accumulation

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

Adhesion
- Membrane changes
- Granule secretion
- Glycoprotein (GP) IIb/IIIa expression
- Multiple agonists
- Feedback loops

Factors Contributing to Platelet Activation and Thrombus Formation

- vWF
- GP IIb/IIIa-mediated
- Fibrogen
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/m² (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%)

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

PAR: population attributable risk
Apopt: apolipoprotein

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
  - Noninvasive Testing (EET, nuclear, stress echo, 64 slice computed tomography, others)
  - Intermediate Risk
    - Noninvasive Testing
  - High Risk
    - Weight Loss Is the Most Important
    - Healthy diet
    - Exercise

Risk Category

- Low Risk
- Intermediate Risk
- High Risk

Weight Loss Is the Most Important Healthy diet Exercise

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>High Risk</td>
<td>&lt; 100 mg/dL (or &lt; 70 mg/dL)</td>
<td>≥ 100 mg/dL</td>
</tr>
<tr>
<td></td>
<td>≥ 100 mg/dL (&lt; 100 mg/dL; consider drug options)</td>
<td></td>
</tr>
<tr>
<td>Moderately High Risk</td>
<td>&lt; 130 mg/dL</td>
<td>≥ 130 mg/dL</td>
</tr>
<tr>
<td></td>
<td>≥ 130 mg/dL (100-129 mg/dL; consider drug options)</td>
<td></td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>&lt; 130 mg/dL</td>
<td>≥ 130 mg/dL</td>
</tr>
<tr>
<td>Lower Risk</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


NCEP-ATP III: Pharmacological Reduction of Cardiovascular Risk

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>&lt; 100 mg/dL (or &lt; 70 mg/dL)</td>
<td>≥ 100 mg/dL</td>
</tr>
<tr>
<td></td>
<td>≥ 100 mg/dL (100-129 mg/dL; consider drug options)</td>
<td></td>
</tr>
<tr>
<td>Moderately high risk</td>
<td>&lt; 130 mg/dL</td>
<td>≥ 160 mg/dL</td>
</tr>
<tr>
<td></td>
<td>≥ 160 mg/dL (160-189 mg/dL; LDL-lowering drug optional)</td>
<td></td>
</tr>
<tr>
<td>Lower risk</td>
<td>&lt; 160 mg/dL</td>
<td>≥ 160 mg/dL</td>
</tr>
</tbody>
</table>

- A high-risk patient with high triglycerides or low high-density lipoprotein-cholesterol (HDL-C), and in combination with fibrates or niacin, should consider LDL-lowering therapy with fibrates or niacin, and LDL-lowering therapy in a high-risk or moderately high-risk patient should reduce LDL-C by 30%-40%.

CHS: Severity of Carotid Stenosis Correlates With Low Ankle-Arm Index

Ankle-arm index

Relative risk of carotid disease

Degree of carotid stenosis

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/m(^2))</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>Receiving Aspirin</td>
<td>1.51</td>
<td>(1.01-2.29)</td>
<td>0.04</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>1.61</td>
<td>(1.07-2.39)</td>
<td>0.002</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 \(_2\alpha\)

Genetic Polymorphisms:
- COX-1
- GP IIa receptor
- Collagen receptor
- VWF receptor

Clinical Factors:
- Insufficient suppression of cyclooxygenase (COX)-1
- Overexpression of COX-2
- Messenger ribonucleic acid
- Increased norepinephrine
- Generation of 8-iso-PGF \(_2\alpha\)

Irbesartan: Early afternoon plasma irbesartan concentrations after dosing every 12 hours: Mean (95% CI)

<table>
<thead>
<tr>
<th>Hour</th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.20</td>
<td>(1.10-1.30)</td>
</tr>
<tr>
<td>12</td>
<td>0.80</td>
<td>(0.70-0.90)</td>
</tr>
<tr>
<td>24</td>
<td>0.60</td>
<td>(0.50-0.70)</td>
</tr>
</tbody>
</table>


Oral Antiplatelet Agents

- Thromboxane A₂ (TXA₂) inhibitor:
  - Acetylsalicylic acid (ASA)
- Phosphodiesterase inhibitor:
  - Dipyridamole
  - Cilostazol
- ADP-receptor antagonists:
  - Clopidogrel
  - Ticlopidine

Oral Antiplatelet Agents: Mechanisms of Action

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)

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
- 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 antplatelet therapy
- 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)

Risk of Stroke Increases Dramatically With Atherothrombosis

<table>
<thead>
<tr>
<th>Preceding Event</th>
<th>AMI 5 to 7 fold (includes death)</th>
<th>Stroke 2 to 4 fold (includes TIA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI</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 (includes TIA)</td>
</tr>
<tr>
<td>Peripheral Vascular</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)

Aspirin
Clopidogrel

P = 0.043

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


ESPS2: Stroke Prevention With Combined Aspirin and Dipyridamole

2-year incidence of stroke

ASA
Dipyridamole
ASA+Dipyridamole

p = 0.013
p = 0.039
p < 0.001

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

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

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

Placebo plus clopidogrel
Aspirin plus clopidogrel

P = 0.244

ESPRIT: Aspirin Plus Dipyridamole Reduces Primary Outcome


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

PRoFESS: Comparison of Antiplatelet Regimens in Stroke Recurrence


- Aspirin plus ERDP: 5.3% recurrence
- Clopidogrel: 4.9% recurrence

HR 1.08 (95% CI, 0.96-1.22)

AHA/ASA Recommendations for Antiplatelet Therapy


- Class I Recommendations
  - 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 (30-325 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).


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**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.


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**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.

GUSTO-IIb Study: ACS Mortality at Six Months Based on Initial ECG Findings


Polling Question

What is the appropriate loading dose of clopidogrel prior to PCI?

A. 75 mg  
B. 150 mg  
C. 300 mg  
D. 600 mg  
E. We are still trying to figure this one out!

CURE: Clopidogrel Improves Cardiovascular Outcomes


Clopidogrel increased major bleeding (RR 1.38; P = 0.001), but not life-threatening bleeding (RR 1.21; P = 0.13).
**CURE-PCI: Clopidogrel Following PCI Reduces Cardiovascular Outcomes**

<table>
<thead>
<tr>
<th>Days of follow-up</th>
<th>Placebo</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>10</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>20</td>
<td>0.10</td>
<td>0.15</td>
</tr>
<tr>
<td>30</td>
<td>0.15</td>
<td>0.20</td>
</tr>
</tbody>
</table>

No significant between-group difference in major bleeding ($P = 0.99$).

**CREDO: Decrease in Ischemic Events With Clopidogrel One Year After PCI**

**CLARITY: Clopidogrel Before PCI in ST-Elevation Myocardial Infarction**

There was no significant increase in the rates of major or minor bleeding with clopidogrel compared to no pretreatment (2.0% vs 1.9%; $P > 0.99$).

<table>
<thead>
<tr>
<th>Number of Risk</th>
<th>Months from randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>993 (353)</td>
</tr>
<tr>
<td>Placebo</td>
<td>993 (353)</td>
</tr>
</tbody>
</table>

Relative risk reduction: $-26.9\%$ ($P = 0.02$).

<table>
<thead>
<tr>
<th>Days after randomization</th>
<th>No pretreatment</th>
<th>Clopidogrel pretreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>2.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>10</td>
<td>3.0%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

There was no significant increase in the rates of major or minor bleeding with clopidogrel compared to no pretreatment (2.0% vs 1.9%; $P > 0.99$).
CLARITY: Clopidogrel Reduces Risk of Cardiovascular Death Before or After PCI

Odds Ratio (95% CI)

0.70 (0.48-1.02)

PCI-CURE CREDO PCI-CLARITY Overall

P = 0.005

Risk of myocardial infarction before PCI

Odds Ratio (95% CI)

0.65 (0.43-0.98) 0.83 (0.57-1.21) 0.60 (0.38-0.96) 0.71 (0.56-0.89)

PCI-CURE CREDO PCI-CLARITY Overall

P = 0.004

Risk of cardiovascular death or myocardial infarction after PCI to 30 days

Triton-TIMI: Prasugrel Significantly Reduces Ischemic Events

Increased risk of major bleeding was associated with prasugrel

COMMIT: Clopidogrel Plus Aspirin Reduces Mortality After AMI


Increased risk of major bleeding was associated with prasugrel

Meta-Analysis: Evidence Favoring Loading Doses > 300 mg


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 ($P = 0.003$)

Favors Low Loading

Favors High Loading

0.1 0.2 0.5 1 2 5 10

Randomized Trials

<table>
<thead>
<tr>
<th></th>
<th>High Loading (n)</th>
<th>Standard Loading (n)</th>
<th>Favoring High Loading</th>
<th>Favoring Low Loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALBION (2005)</td>
<td>2/68</td>
<td>15/129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLEAR PLATELETS(2005)</td>
<td>1/60</td>
<td>5/140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gurbel, et al. (2005)</td>
<td>0.52</td>
<td>0.138</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muller, et al. (2001)</td>
<td>0.10</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>502</td>
<td>538</td>
<td></td>
<td></td>
</tr>
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</table>

Nonrandomized Trials

<table>
<thead>
<tr>
<th></th>
<th>High Loading (n)</th>
<th>Standard Loading (n)</th>
<th>Favoring High Loading</th>
<th>Favoring Low Loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seyfarth, et al. (2003)</td>
<td>0/11</td>
<td>0/21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>353</td>
<td>174</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total: All Studies (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>High Loading (n)</th>
<th>Standard Loading (n)</th>
<th>Favoring High Loading</th>
<th>Favoring Low Loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal (95% CI)</td>
<td>502</td>
<td>612</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

OASIS 7 Will Evaluate Dosing Regimens for Clopidogrel and Aspirin in ACS

- A randomized, 2 x 2 factorial study in patients with ST- or non-ST-segment elevation ACS:
  - Patients treated with early invasive therapy with planned catheterization and PCI
  - Clopidogrel regimen: 600 mg loading dose (day 1), 150 mg daily; Aspirin regimen: 150 mg daily (days 1-7), 75 mg daily (days 8-30)
  - Standard regimen: 300 mg loading dose (day 1), 75 mg daily (days 2-30)

- Aspirin regimen: High dose (300-325 mg daily), low dose (75-100 mg daily)

Primary outcomes: first occurrence of any component of cardiovascular death, myocardial infarction, or stroke up to day 30

Secondary outcomes: first occurrence of cardiovascular death, myocardial infarction, stroke, or refractory ischemia up to day 30; individual efficacy outcomes up to day 30: cardiovascular death, total death, myocardial infarction, periprocedural myocardial infarction, stroke, recurrent ischemia, urgent rehospitalization, and treated thrombolysis

- Rates of occluded versus open infarct-related artery at the start of coronary angiography or at hospital discharge, whichever comes first

**AHA/ACC 2006 Guidelines for Antiplatelet Agents**

**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

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**AHA/ACC 2006 Guidelines for Antiplatelet Agents (Continued)**

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)

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**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

Polling Question

When considering the mortality associated with PAD and other atherothrombotic disease states:

A. AMI has a higher mortality than PAD
B. PAD has a higher mortality than AMI
C. Mortality from PAD and AMI are about equal
D. PAD has a higher mortality than stroke

Mortality of Patients Diagnosed With PAD Compared to Myocardial Infarction or Stroke

- Annual mortality was higher in patients with PAD than in patients with myocardial infarction
- Myocardial infarction
- PAD
- Stroke

**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

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**CAPRIE: Reduction of Vascular Events With Clopidogrel or Aspirin**

<table>
<thead>
<tr>
<th>RR Reduction (%) (95% CI)</th>
<th>Clopidogrel better</th>
<th>Aspirin better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>10.7%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>8.6%</td>
<td>7.6%</td>
</tr>
<tr>
<td>PAD</td>
<td>7.6%</td>
<td>7.3%</td>
</tr>
<tr>
<td>All patients</td>
<td>8.6%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk of Cardiovascular Death/Myocardial Infarction/Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Prior Myocardial Infarction</td>
</tr>
<tr>
<td>Prior Ischemic Stroke</td>
</tr>
<tr>
<td>Prior PAD</td>
</tr>
<tr>
<td>Entire Cohort</td>
</tr>
</tbody>
</table>

---

**CHARISMA: Dual Therapy With Aspirin and Clopidogrel**

- Prior Myocardial Infarction
- Prior Ischemic Stroke
- Prior PAD
- Entire Cohort

- Placebo
- Clopidogrel

- HR
- P Value

**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 (%)

Treatment time (weeks)

* $P < 0.05$ at all time points

Cilostazol 100 mg BID
Pentoxifylline 400 mg TID
Placebo

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).

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

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

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

Pharmacological
- Antiplatelet therapy: – ASA – Clopidogrel

Lifestyle Changes Effectively Decrease Platelet Activation

<table>
<thead>
<tr>
<th>Thrombogenic Markers</th>
<th>Physical Exercise</th>
</tr>
</thead>
<tbody>
<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 antplatelet agents has been proven to play an important role in the secondary prevention of atherothrombotic events in stroke, ACS, and PAD.