Anti-platelet therapies and dual inhibition in practice

Therapeutics; Sept. 25th 2007

• Craig Williams, Pharm.D.

• Associate Professor of Pharmacy
Objectives

1. Understand the pharmacology of thienopyridine agents and how their anti-platelet effect pharmacologically compliment both aspirin and GP IIa/IIIb antagonists
2. Describe the relationship between ischemic risk and ischemic event rate reduction with antiplatelet therapy in patients with and without cardiovascular heart disease.
3. Know the epidemiology of both aspirin and clopidogrel resistance
4. Understand the magnitude of both the cardiovascular (CV) risk reduction and the increased bleeding risk of dual antiplatelet therapy.
5. Understand the concept of why stents are used and why drug eluting stents were developed
6. Differentiate the timecourse of recurrent cardiovascular events with antiplatelet therapy in percutaneous coronary intervention (PCI) patients receiving drug-eluting stents (DES) compared to bare metal stents.
7. Understand where the 2006 AHA/ACC guidelines for antiplatelet therapy in patients with cardiac disease and correct and where they are already incorrect
Antiplatelet therapies in ACS

**Oral antiplatelet therapy**
- Aspirin
- Clopidogrel
- Ticlopidine

**IV GP IIb/IIIa inhibition**
- Abciximab
- Eptifibatide
- Tirofiban

**Oral GP IIb/IIIa inhibitors**
- Chromofiban
- Kleryval
- Lefradafiban
- Lotrafiban
- Orbofiban
- Roxifiban
- Sibrafiban
- Xemilofiban

Acute and chronic vascular disease
Acute myocardial vascular disease

Not used in U.S.
Plavix and Ticlid chemically similar. Classed as ‘thienopyridines’. May actually have same active biometabolite

![Ticlopidine](image)

![Clopidogrel](image)

**Figure 1.** Structure of ticlopidine and clopidogrel.
Editorials

Clopidogrel Pharmacogenetics: Promising Steps Towards Patient Care?

Amber L. Beitelshees; Howard L. McLeod

ATVB 2006;26:1681-83
AA: Arachadonic acid
Cox: Cyclooxygenase; TXA₂: Thromboxane A₂
Antithrombotic therapies: Main sites of action

- Tissue factor
  - Coagulation cascade
    - Prothrombin
      - Factor Xa
        - (AT)
      - Thrombin
        - Fibrinogen
          - Fibrin
            - Platelet aggregation
              - Thrombus
            - GP IIb/IIIa inhibitors
        - Fibrinogen cross-linking at GP IIb/IIIa
          - Platelet activation: GP IIb/IIIa receptor expressed
            - Thromboxane A₂
              - ADP
                - Aspirin
        - Collagen
          - Thienopyridines

- LMWH
- Heparin
- Pentasaccharides
- Warfarin
- Direct thrombin inhibitors
How effective is anti-platelet monotherapy?
Depends on the risk of the population being treated
ASA: The benefit of anti-platelet therapy is greater in higher risk patients and quite low in low risk patients

Carlo Patrono, Barry Coller, Garret A. FitzGerald, Jack Hirsh, and Gerald Roth
CHEST 2004;126: 234S-264S.

2 Events prevented per 1000 treated in healthy population
Case for CVD prevention with ASA in moderate risk patients not so clear

FDA committee votes not to approve aspirin for the primary prevention of MI

Tue, 09 Dec 2003 21:00:00 Michael O'Riordan

Gaithersburg, MD - The evidence supporting the use of aspirin for the primary prevention of MI failed to hold up to the scrutiny of the FDA's Cardiovascular and Renal Drugs Advisory Committee at its most recent December 8, 2003 meeting.

The committee voted overwhelmingly 11 votes against and three votes for approval of the petition sought by Bayer Corp to approve aspirin for the reduction of the risk of a first MI in moderate-risk patients, those with a 10-year coronary heart disease risk of < 20%

Despite the existing data, which consisted of five major clinical trials, the committee felt the evidence supporting the extended label for aspirin was inconsistent at best or lacking at worst.

www.theheart.org
Benefits of antiplatelet therapy in low-risk patients offset by major bleeding episodes

Figure 4. Benefits and Risks of Low-Dose Aspirin in Primary-Prevention Trials.
Bleeding Definitions: GUSTO Criteria

• Severe or major bleeding:
  • Fatal bleeding
  • Primary or post-traumatic intracranial hemorrhage
  • Substantial hemodynamic compromise requiring treatment to sustain cardiac output
• Moderate:
  • Bleeding required transfusion but did not result in hemodynamic compromise
• Minor bleeding:
  • Other bleeding, not requiring transfusion or causing hemodynamic compromise

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- Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely. I (B)
Combining anti-platelet therapy conceived due to limitations of ASA in clinical trials and then bolstered by concerns about ASA resistance
The clinical mystery of ASA resistance

EDITORIAL COMMENT
Aspirin Resistance: A New Independent Predictor of Vascular Events?*
John W. Eikelboom, MBBS, MSc, FRACP, FRCPA,†‡ Graeme J. Hankey, MBBS, MD, FRCP, FRCP EDIN, FRACP‡§
Perth, Australia

J Am Coll Cardiol 2003;41:966-8

EDITORIAL COMMENT
Platelet Function
Assessment to Predict Outcomes After Coronary Interventions
Hype or Hope?*
Fernando Alfonso, MD, PhD, FESC,†
Dominick J. Angiolillo, MD, PhD, FACC‡
Madrid, Spain; and Jacksonville, Florida

J Am Coll Cardiol 2006;48:1751-4

EDITORIAL COMMENT
Aspirin Resistance: More Than Just a Laboratory Curiosity*
Deepak L. Bhatt, MD, FACC, FSCAI, FESC
Cleveland, Ohio

J Am Coll Cardiol 2004;43:1127-9

EDITORIAL COMMENT
On Defining Aspirin Resistance*
David J. Schneider, MD, FACC
Burlington, Vermont

J Am Coll Cardiol 2006;48:577-79
Frequency of Aspirin Resistance in a Community Hospital

Ahmadshah Mirkhel, MD\textsuperscript{a}, Eliot Peyster, BS\textsuperscript{c}, James Sundeen, MD\textsuperscript{b}, Linda Greene, MD\textsuperscript{a}, Alan D. Michelson, MD\textsuperscript{e}, Ahmed Hasan, MD, PhD\textsuperscript{d}, and Michael Domanski, MD\textsuperscript{c},\textsuperscript{*}

• Used VerifyNow - a commercially available system - to test ability of activated platelets to bind fibrinogen

• Repeated optical measurements of coagulating blood which reports aspirin resistant units (ARU): >550 ARU consistent with no ASA effects

• 123 patients tested

RESULTS

• 12\% resistant to 81mg ASA and 5\% resistant to 325mg
Clopidogrel response is variable and increasing the dose to 600 mg from standard 300 mg shifts the dose-response. N = 190

Δ Platelet aggregation (5 µM ADP-induced) at 24 hours

Increasing the dose of ASA increases the bleeding risk but does not increase the clinical benefit

<table>
<thead>
<tr>
<th>Aspirin Dose (mg/day)</th>
<th>OR for Vascular Events</th>
<th>Aspirin Dose (mg/day)</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;75</td>
<td>0.87</td>
<td>75-100</td>
<td>1.9%</td>
</tr>
<tr>
<td>75-150</td>
<td>0.68</td>
<td>100-199</td>
<td>2.8%</td>
</tr>
<tr>
<td>160-325</td>
<td>0.76</td>
<td>200-325</td>
<td>3.7%</td>
</tr>
<tr>
<td>&gt;325</td>
<td>0.81</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Recommended Dose**
160-325 mg chewed or crushed for first dose
75-160 mg daily thereafter

CAPRIE study:
Clopidogrel versus ASA about a tie

Patients with a recent ischemic stroke or MI, or symptomatic PAD

n=19,185 followed for 1.9 years

Cumulative event rate* (%)

0 3 6 9 12 15 18 21 24 27 30 33 36

Months of follow-up

ASA

Clopidogrel

8.7%† RRR
(p=0.043)

0.5% fewer events*/yr

NNT=200
Cost of $292,000 @ clopidogrel cost of $2/dose

*events: stroke, MI or vascular death

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_Circulation_. 2006;113:2363-2372
Clopidogrel in Unstable angina to prevent
Recurrent Events
ASA+Plavix superior to ASA alone but
benefit occurs early


*MI, stroke or cardiovascular death
†On a background of standard therapy (including ASA)

ARR: 2.1%, NNT=48
CURE: Bleeding complications

Major bleeding: 5.1% vs. 2.4% (p<0.001)

Life-threatening: 3.7% vs. 2.7%

Non-life-threatening: 1.38 (1.13–1.67) vs. 1.21 (0.95–1.56) (p = 0.001)

Relative risk

So CURE trial showed benefit in acute coronary syndromes that outweighed benefit. What about chronic stable vascular disease?
CHARISMA Inclusion Criteria

Pts aged ≥45 years with >1 of the following:

1) Documented coronary disease
   or
2) Documented cerebrovascular disease
   or
3) Documented symptomatic PAD (peripheral arterial disease)
   or
4) 2 major or 1 major and 2 minor or 3 minor risk factors

Overall Population: Primary Efficacy Outcome (MI, Stroke, or CV Death)

Placebo + ASA*
7.3%

Clopidogrel + ASA*
6.8%

RRR: 7.1% [95% CI: -4.5%, 17.5%]
P=0.22

CHARISMA: Primary Efficacy Outcome (MI/Stroke/CV Death) by Category of Inclusion

CAD, CVD or PAD (N=12,153)

- Placebo + ASA*: 7.9%
- Clopidogrel + ASA*: 6.9%
- RRR: 12.5% [95% CI: 0.2%, 23.2%]
- p=0.046

Multiple Risk Factor (N=3,284)

- Placebo + ASA*: 5.5%
- Clopidogrel + ASA*: 6.6%
- RRR: -20% [95% CI: -58.8%, 9.3%]
- p=0.20

Ave. follow-up: 28 mo.

### CHARISMA: Overall Population: Safety Results

<table>
<thead>
<tr>
<th>Safety Outcome* - N (%)</th>
<th>Clopidogrel + ASA (n=7802)</th>
<th>Placebo + ASA (n=7801)</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>GUSTO Severe Bleeding</td>
<td>130 (1.7)</td>
<td>104 (1.3)</td>
<td>1.25 (0.97, 1.61)</td>
<td>0.09</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>26 (0.3)</td>
<td>17 (0.2)</td>
<td>1.44 (0.79, 2.63)</td>
<td>0.23</td>
</tr>
<tr>
<td>Primary ICH</td>
<td>26 (0.3)</td>
<td>27 (0.4)</td>
<td>0.93 (0.54, 1.58)</td>
<td>0.78</td>
</tr>
<tr>
<td>GUSTO Moderate Bleeding</td>
<td>164 (2.1)</td>
<td>101 (1.3)</td>
<td>1.62 (1.27, 2.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GUSTO Minor Bleeding</td>
<td>not reported</td>
<td></td>
<td></td>
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*Adjudicated outcomes by intention to treat analysis
ICH= Intracranial Hemorrhage

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Dual Antiplatelet therapy for Percutaneous Coronary Intervention (PCI): The Stent Story
“In 1991, Surrusys and colleagues reported a 24% incidence of thrombotic stent occlusion within 6 months after implantation…”
What is the problem with DES: after deployment any stent remains thrombogenic if in contact with whole blood.

Thrombotic risk greatly decreased when stent is fully epithelialized (incorporated into wall of blood vessel)
30-days post stent deployment, bare metal stent is well epithelialized while various drug eluting stents (DES) are less incorporated into vessel wall

Bare metal       sirolimus       paclitaxel       pimecrolimus

Transcatheter Cardiovascular Therapeutics meeting (TCT), 2006; abstract #4534
Expedited Review

Late Clinical Events After Clopidogrel Discontinuation May Limit the Benefit of Drug-Eluting Stents: An Observational Study of Drug-Eluting Versus Bare-Metal Stents (BASKET-LATE): 746 patients with 1,133 stented lesions followed for 18 months (6 months of Plavix followed by 12 months off Plavix) shows different time course of CV events with bare metal vs. DES

![Graph showing comparison of death/non-fatal MI between BMS and DES](image)

- BMS: 1.3%
- DES: 4.9%
- p = 0.01

JACC 2005;48:2584-91
Update to FDA Statement on Coronary Drug-Eluting Stents:

On September 14, 2006, FDA issued an initial statement related to concerns about adverse events related to coronary drug-eluting stents (DES) with the currently approved CYPHER and the TAXUS stent.

- Both approved DES are associated with a small increase in stent thrombosis compared to bare metal stents that emerges 1 year post-stent implantation.
- The concerns about thrombosis do not outweigh the benefits of DES compared to bare metal stents when DES are implanted within the limits of their approved indications for use.

Regarding the duration of antiplatelet therapy:
- Data from several studies suggests that a longer duration of antiplatelet therapy than is currently included in the CYPHER and TAXUS labeling may be beneficial.
- The optimal duration of antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy.
- The labeling for both approved DES should include reference to the ACC/AHA/SCAI PCI Practice Guidelines, which recommend that patients receive aspirin indefinitely plus a minimum of 3 months (for Cypher patients) or 6 months (for TAXUS patients) of clopidogrel, with therapy extended to 12 months in patients at a low risk of bleeding.
Stent Thrombosis Redux — The FDA Perspective

Andrew Farb, M.D., and Ashley B. Boam, M.S.

Dr. Farb - Medical Officer, Devices Branch. FDA

Dr. Boam – Chief, Interventional Cardiology, Devices Branch. FDA
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