Oral Antiplatelet Therapy

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Financial Disclosures

- Boston Scientific
- Gilead
“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”
Thrombus Formation

Two key elements: **cellular** (platelets) and **plasmatic** (coagulation factors)
ANTITHROMBOTIC DRUGS USED IN ACS/PCI

I. ANTIPLATELET DRUGS
- COX-1 inhibitor (aspirin)
- P2Y₁₂ inhibitors (ticlopidine; clopidogrel; prasugrel; ticagrelor)
- Glycoprotein IIb/IIIa inhibitors (abciximab; eptifibatide; tirofiban)

II. ANTICOAGULANT DRUGS
- Anti-Factor II (anti-thrombins)
  - Indirect Thrombin Inhibitors (UFH & LMWH)
  - Direct Thrombin Inhibitors (Bivalirudin)
- Anti-Factor X
  - Fondaparinux
1. Which drugs do we use?
2. When to start and at which dose?
3. Length of therapy?
The combination of aspirin and a P2Y12 receptor inhibitor represents the treatment of choice for the prevention of recurrent ischemic events, including stent thrombosis.
Mechanisms of Action of Oral Antiplatelet Therapies

ADP = adenosine diphosphate, TXA2 = thromboxane A2, COX = cyclooxygenase.

Ticlopidine during PCI with use of Coronary Stents

- Urban et al, Circulation 1998
- Bertrand et al, Circulation 1998
- Leon et al, Circulation 1998
The Thienopyridine Family

Ticlopidine

\[ \text{Ticlopidine} \]

(1st generation)

- P2Y\textsubscript{12} ADP receptor antagonism: antithrombotic treatment of choice for coronary stenting
- Delayed time frame to achieve full antiplatelet effects
- Side effects: neutropenia, thrombocytopenia, rash, diarrhea, etc

Clopidogrel

\[ \text{Clopidogrel} \]

(2nd generation)

- Better Safety profile - Fewer side effects
  - Better clinical outcomes
  - Solution to these problems:
  - Rapid onset of action with a loading dose
  - (Bhatt DL et al. J Am Coll Cardiol 2002; 39: 9–14.).
Primary Endpoint—MI/Stroke/CV Death

The primary outcome occurred in 9.3% of pts in the clopidogrel + ASA group and 11.4% in the placebo + ASA group.

*Other standard therapies were used as appropriate.
Strategies of ADP P2Y12 mediated platelet inhibition
Balance of Efficacy and Safety

CV Death / MI / Stroke

Prasugrel: HR 0.81 (0.73-0.90), P=0.0004, NNT = 46

Clopidogrel: HR 1.32 (1.03-1.68), P=0.03, NNH = 167

TIMI Major

Prasugrel: HR 1.32 (1.03-1.68), P=0.03, NNH = 167

NonCABG Bleeds
Novel P2Y12 receptor antagonists: When “NOT to Use” or “Use with Caution”? 

– Prasugrel.
Contraindicated: high-risk bleeding; prior TIA/stroke; hypersensitivity

Precautions: elderly (>75y), low-weight (<60kg); CABG/surgery (7days).

– Ticagrelor.
Contraindicated: high-risk bleeding; prior hemorrhagic stroke; severe hepatic dysfunction

Precautions: compliance (b.i.d. administration), drug interactions (CYP 3A4 interfering agents); regional differences (North America/ASA dose <100mg), COPD/asthma, bradyarrhythmia, gout syndromes, CABG/surgery (5 days).
Oral Antiplatelet Therapy in ACS/PCI

1. Which drugs should we use?

2. When to start and at which dose?

3. Length of therapy?
“An aspirin a day will help prevent a heart attack if you have it for lunch instead of a cheeseburger.”
Patients already taking daily aspirin therapy should take 81 to 325 mg prior to PCI.

Patients not on aspirin therapy should be given nonenteric aspirin 325 mg prior to PCI.

After PCI, aspirin should be continued indefinitely.
After PCI, it is reasonable to use 81 mg per day of aspirin in preference to higher maintenance doses.
Antithrombotic Trialists’ Collaboration

Different Doses of Aspirin vs Control

<table>
<thead>
<tr>
<th>Daily Dose</th>
<th>Aspirin</th>
<th>Control</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asp 500-1500</td>
<td>14.5%</td>
<td>17.2%</td>
<td>19%±3</td>
</tr>
<tr>
<td>Asp 160-325</td>
<td>11.5%</td>
<td>14.8%</td>
<td>26%±3</td>
</tr>
<tr>
<td>Asp 75-150</td>
<td>11.0%</td>
<td>15.2%</td>
<td>32%±6</td>
</tr>
<tr>
<td>Asp &lt;75</td>
<td>17.3%</td>
<td>19.4%</td>
<td>13%±8</td>
</tr>
<tr>
<td>Any aspirin</td>
<td>12.9%</td>
<td>16.1%</td>
<td>23%±2</td>
</tr>
</tbody>
</table>

*(2P<0.00001)*

*BMJ 2002;324:71-86*
P2Y12 Inhibitors
A loading dose of a P2Y$_{12}$ receptor inhibitor should be given to patients undergoing PCI with stenting. Options include:

- Clopidogrel 600 mg (ACS and non-ACS patients).
- Prasugrel 60 mg (ACS patients).
- Ticagrelor 180 mg (ACS patients).
Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely.

In patients requiring warfarin, clopidogrel, and aspirin therapy after PCI, an INR of 2.0 to 2.5 is recommended with low dose aspirin (75 mg to 81 mg) and a 75-mg dose of clopidogrel.
Bleeding risk in PCI patients on dual antiplatelet therapy requiring oral anticoagulation

Bleeding event free survival

† Log Rank, p<0.0001 vs dual therapy
‡ Log Rank, p<0.0001 vs triple therapy (INR: 2.0-2.5)

Rossini & Angiolillo Am J Cardiol 2008
PPIs and Antiplatelet Therapy

PPI should be used in patients with history of prior GI bleeding who require DAPT (In patients in whom there is a clear indication for PPI therapy, some clinicians may choose to use a PPI other than omeprazole).

PPI use is reasonable in patients with increased risk of gastrointestinal bleeding (advanced age, concomitant use of warfarin, steroids, NSAIDS, H pylori infection, etc.) who require DAPT.

Routine use of a PPI is not recommended for patients at low risk of gastrointestinal bleeding, who have much less potential to benefit from prophylactic therapy.
2009 Updated Labeling for Clopidogrel–PPI Interaction

- FDA-required label changes:²
  - Warning: “Co-administration of Plavix with omeprazole, a proton pump inhibitor that is an inhibitor of CYP2C19, reduces the pharmacological activity of Plavix if given concomitantly or if given 12 hours apart”
  - Drug-Drug Interactions: “Avoid concomitant use of drugs that inhibit CYP2C19, including omeprazole, esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine”
  - Based on PK/PD studies showing concomitant omeprazole reduced clopidogrel active metabolite and effect on platelets¹
    - Did not include COGENT study data²
- EMEA warning extends to discourage concomitant use of all PPIs³
  - Concomitant use of drugs that inhibit CYP2C19 discouraged; concomitant use of any PPI “should be avoided unless absolutely necessary”⁴

EMEA=European Medicines Agency; FDA=Food and Drug Administration; PD=pharmacodynamic; PK=pharmacokinetic.
Oral Antiplatelet Therapy in PCI

1. Which drugs should we use?
2. When to start and at which dose?
3. Length of therapy?
After PCI, aspirin should be continued indefinitely.

The duration of P2Y\textsubscript{12} inhibitor therapy after stent implantation should generally be as follows:

a) In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y\textsubscript{12} inhibitor therapy should be given for at least 12 months (clopidogrel 75 mg daily); prasugrel 10 mg daily; and ticagrelor 90 mg twice daily.

b) In patients receiving a DES for a non-ACS indication, clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding.

c) In patients receiving a BMS for a non-ACS indication, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks).
Patients should be counseled on the importance of compliance with DAPT, and that therapy should not be discontinued before discussion with the relevant cardiologist.

After PCI, it is reasonable to use 81 mg per day of aspirin in preference to higher maintenance doses.

If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of $\text{P2Y}_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (e.g., >12 months) of $\text{P2Y}_{12}$ inhibitor therapy is reasonable.
Continuation of clopidogrel, prasugrel or ticagrelor beyond 12 months may be considered in patients undergoing DES placement.
Platelet Function and Genetic Assays & Antiplatelet Drug Response
Platelet function testing may be considered in patients at high risk for poor clinical outcomes.

In clopidogrel-treated patients with high platelet reactivity, alternative agents, such as prasugrel or ticagrelor, might be considered.

The routine clinical use of platelet function testing to screen clopidogrel-treated patients undergoing PCI is not recommended.
Genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel.

When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with an alternate P2Y$_{12}$ inhibitor (e.g., prasugrel or ticagrelor) might be considered.

The routine clinical use of genetic testing to screen clopidogrel-treated patients undergoing PCI is not recommended.
Aspirin Resistant Patient Management

- Educate patient on importance of compliance
- Eliminate interfering substances (ibuprofen)
- Increase aspirin dose (?) *(increasing the dose of aspirin does not enhance COX-1 inhibition)*
- Increase dose regimen from once to twice daily administration (?) *(overcome platelet turnover)*
- Add or switch antiplatelet treatment (?)
Questions?