Oral Antiplatelet Therapy in PCI/ACS

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Basic Concepts
Thrombus Formation

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

I. ANTIPLATELET DRUGS
   • Aspirin
   • Thienopyridines
     • Glycoprotein IIb/IIIa inhibitors

II. ANTITHROMBIN DRUGS
   • Indirect Thrombin Inhibitors
     Unfractionated heparin
     LMWH
   • Direct Thrombin Inhibitors
     Bivalirudin
1. Which drugs should we use?

2. When to start and at which dose?

3. Length of therapy?
1. Which drugs should we use?

2. When to start and at which dose?

3. Length of therapy?
Mechanisms of Action of Oral Antiplatelet Therapies

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

Long-term Efficacy of ASA in Reducing Death or MI in Patients with Unstable Angina

Wallentin LC et al JACC 1991;18:1587–1593

Placebo

ASA 75 mg

Risk ratio after 1 year 0.52
95% CI 0.37–0.72 (p=0.0001)
Benefit of Long-Term Aspirin After PCI: M-HEART II

660 patients randomized to placebo, daily ASA or the thromboxane A$_2$ receptor inhibitor sulotroban for 6 months following PTCA.

![Bar chart showing the percentage of non-PCI related MI at 6 months for ASA, thromboxane A$_2$ receptor inhibitor, and placebo.](chart)

- ASA: 1.2%
- Thromboxane A$_2$ Receptor Inhibitor: 1.8%
- Placebo: 5.7%

Mean interval between PCI and myocardial infarction: 37 ± 31 days

P = 0.03 compared with ASA or thromboxane receptor inhibitor

Savage MP Circulation 1995;92:3194
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

\[ \text{Thienopyridine Family} \]

\[ \text{1st generation} \]

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

Solution to these problems:

- **Better Safety profile - Fewer side effects**
- **Rapid onset of action with a loading dose**
- **Better clinical outcomes**
  (Bhatt DL et al. *J Am Coll Cardiol* 2002; 39: 9–14.).
Synergistic Antithrombotic Effect of Clopidogrel Plus Aspirin in Humans

Oral Antiplatelet Therapy in PCI/ACS

1. Which drugs should we use?

2. When to start and at which dose?

3. Length of therapy?
Aspirin
Patients already taking daily chronic ASA therapy should take 75 mg to 325 mg ASA before the PCI procedure is performed.

Patients not already taking daily chronic ASA therapy should be given 300 to 325 mg of aspirin at least 2 hours and preferably 24 hours before the PCI procedure is performed.
After the PCI procedure, in patients with neither ASA resistance, allergy, nor increased risk of bleeding, ASA 325 mg daily should be given for at least 1 month after bare-metal stent implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which daily chronic ASA use should be continued indefinitely at a dose of 75 to 162 mg.
What is the Correct Dose of Aspirin in the Peri-PCI Setting?

• Only one randomized trial has investigated different doses of aspirin peri-PTCA and clinical outcomes (No difference between 80mg and 1500mg QD among 495 patients. *J Am Coll Cardiol*. 1988;11:236A)

• Almost all trials of percutaneous coronary intervention have either mandated or recommend a daily aspirin be given as 325mg daily.
## 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**
Aspirin Dose and Incidence of Major Bleedings

Insights from CURE

A loading dose of clopidogrel should be administered before PCI is performed. An oral loading dose of 300 mg, administered at least 6 hours before the procedure, has the best established evidence of efficacy. Continue with a maintenance dose of 75 mg daily.
Effects of Pre-treatment
One Month Results (Death, MI, UTVR)

**PCI-CURE**

- **N=2658**
- **6.4%** No-PT
- **4.5%** PT
- **30.0% RRR**
  - **P=0.03**

**CREDO**

- **N=2116**
- **8.3%** No-PT
- **6.8%** PT
- **18.5% RRR**
  - **P=0.23**

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**CREDO**

**Effect of Timing of Loading Dose:**

**28 Day Endpoint - Death, MI, UTVR**

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>PT-Clopidogrel*</th>
<th>No-PT*</th>
<th>N</th>
<th>PT-Clopidogrel Better</th>
<th>No-PT Better</th>
<th>RRR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to &lt;6 hrs</td>
<td>7.9</td>
<td>7.0</td>
<td>893</td>
<td></td>
<td></td>
<td>-13.4</td>
<td>NS</td>
</tr>
<tr>
<td>6 to 24 hr</td>
<td>5.8</td>
<td>9.4</td>
<td>851</td>
<td></td>
<td></td>
<td>38.6</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Overall CREDO Results**

| RRR 18.5 | P=0.23 |

- **PT** = Pretreatment
- * Plus ASA and other standard therapies

Clopidogrel Loading Dose Timing and Risk of MACE

Log Odds of Death, MI or UTVR at 28 Days

P = 0.020 for treatment / timing interaction

CURE: CABG-Related Bleeding

% of Pts. Major Bleeding

- <5 days
  - clopidogrel + ASA: 9.6%
  - ASA: 6.3%
  - P = 0.06
- >5 days
  - clopidogrel + ASA: 4.4%
  - ASA: 5.3%
  - P = NS

N = 912

CURE Trial N Engl J Med 2001
If clopidogrel is given at the time of procedure, supplementation with GP IIb/IIIa receptor antagonists can be beneficial to facilitate earlier platelet inhibition than with clopidogrel alone.

For patients with an absolute contraindication to ASA, it is reasonable to give a 300-mg loading dose of clopidogrel, administered at least 6 hours before PCI, and/or GP IIb/IIIa antagonists, administered at the time of PCI.

When a loading dose of clopidogrel is administered, a regimen of greater than 300 mg is reasonable to achieve higher levels of antiplatelet activity more rapidly, but the efficacy and safety compared with a 300-mg loading dose are less established.

It is reasonable that patients undergoing brachytherapy be given daily clopidogrel 75 mg indefinitely and daily aspirin 75 to 325 mg indefinitely unless there is significant risk for bleeding.

Adapted from Smith SC Jr, et al. Available at:
High Clopidogrel Loading Dose Regimen

Activated GP IIb/IIIa (ADP 2µM)

- 300 mg loading dose (n=27)
- 600 mg loading dose (n=23)

% Positive Cells

- Basal
- 4h
- 24h
- 48h

Post - PCI

- p<0.0001
- p=0.001 (MANOVA)
- p=0.009
- p=0.005

ARMDA-2 Trial: Primary endpoint

Primary Composite of death, MI, and TVR at 30 days

Clopidogrel pre-treatment 4-8 hrs before PCI

p = 0.041

Patti G et al. Circulation 2005
ISAR REACT: Abciximab vs. Placebo in Low-Moderate Risk PCI

All patients pretreated with 600mg clopidogrel at least 2 hrs prior to PCI.

30-Day Event Rate (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=1080)</th>
<th>Abciximab (n=1079)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, TVR</td>
<td>4.2</td>
<td>4.0</td>
</tr>
<tr>
<td>Death</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Q MI</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Non-Q MI</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>TVR</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.1</td>
<td>0.7</td>
</tr>
</tbody>
</table>


Pretreatment equally efficacious if initiated 2 to 24 hours prior to a PCI.
ISAR-SWEET: Abciximab vs. Placebo in DM Patients

701 patients with DM (29% on Insulin) undergoing elective PCI pretreated (>2 hrs) with 600 mg clopidogrel.

Abciximab (N=351) vs. Placebo (N=350)

% Death/MI

Months After Randomization

P=0.91

ISAR-REACT 2: Abciximab vs. Placebo in ACS

ACS patients (n=2022) undergoing PCI pretreated (>2 hrs) with 600 mg clopidogrel

Death/MI/UTVR, %

Abciximab vs. Placebo

RR = 0.75 [95% CI, 0.58-0.97]

ISAR-REACT 2: Abciximab vs. Placebo in ACS

Troponin Level & Benefit of Abciximab

Death/MI/UTVR, %

Troponin-Positive: RR=0.71 [0.54-0.95]

Troponin-Negative: RR=0.99 [0.56-1.76]

Days after randomization

In patients in whom subacute thrombosis may be catastrophic or lethal (unprotected left main, bifurcating left main, or last patent coronary vessel), platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg per day if less than 50% inhibition of platelet aggregation is demonstrated.

Only small size platelet function studies available

No safety/efficacy data

Triple versus Dual Antiplatelet Therapy

Role for cilostazol (PDE-III inhibitor) in adjunct to ASA & clopidogrel?

Stent thrombosis @ 30 days (Lee SW et al JACC 2006)

- Triple therapy vs dual therapy
- 9/1597 (0.5%) vs 1/1415 (0.1%) p=0.024

Cilostazol (Pletal): No PCI guideline recommendation

FDA approval only for symptomatic relief of PAD
Oral Antiplatelet Therapy in PCI/ACS

1. Which drugs should we use?

2. When to start and at which dose?

3. Length of therapy?
Long Term Efficacy of Clopidogrel

**PCI-CURE**
Endpoint: Death / MI; N=2658

**CREDO**
Endpoint: Death / MI / Stroke; N=2116


In patients who have undergone PCI, clopidogrel 75 mg daily should be given for at least 1 month after bare-metal stent implantation (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks), 3 months after sirolimus stent implantation, and 6 months after paclitaxel stent implantation, and ideally up to 12 months in patients who are not at high risk of bleeding.

Incidence, Predictors, and Outcome of Thrombosis After Successful Implantation of Drug-Eluding Stents

Univariate Predictors of Cumulative Stent Thrombosis

- Premature Antiplatelet Therapy Discontinuation
- Prior Brachytherapy
- Renal Failure
- Bifurcation with 2 Stents
- Bifurcation Lesion
- Unprotected Left Main Artery
- Diabetes

Incidence of Stent Thrombosis

Hazard Ratio for ATP Discontinuation = 89

Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy

Eugène P McFadden, Eugenio Stabile, Evelyn Regar, Edouard Cheneau, Andrew TL Cing, Timothy Kimmard, William O'Suddath, Neil J Weissman, Rebecca Torguson, Kenneth M Kent, August D Pichard, Lowell F Satler, Ron Waksman, Patrick W Serruys

Although the safety profiles of coronary stents eluting sirolimus or paclitaxel do not seem to differ from those of bare metal stents in the short-to-medium term, concern has arisen about the potential for late stent thromboses related to delayed endothelialisation of the stent struts. We report four cases of angiographically-confirmed stent thrombosis that occurred late after elective implantation of polymer-based paclitaxel-eluting (343 and 442 days) or sirolimus-eluting (335 and 375 days) stents, and resulted in myocardial infarction. All cases arose soon after antiplatelet therapy was interrupted. If confirmed in systematic long-term follow-up studies, our findings have potentially serious clinical implications.

**Clopidogrel for >1-year?**
Adjusted outcomes were analyzed at 24 months.

- Patients in the DES with clopidogrel group had significantly lower rates of death or MI than did patients in the DES without clopidogrel group.

- Among BMS patients, there were no differences in death or MI.

CAPRIE-like cohort from CHARISMA – Prior MI

N = 3,846

HR: = 0.774 [95% CI: (0.613, 0.978)]

p=0.031

Insights from CHARISMA: Timing of Severe or Moderate Bleeding

1. Which drugs should we use?

2. When to start and at which dose?

3. Length of therapy?

Emphasize with your DES treated patients one-year of dual antiplatelet therapy *(follow the guidelines)*, ....... afterwards evaluate on a patient-to-patient basis *(individualized treatment… no guidelines available)*.