Guideline Review
Antiplatelet Therapy after PCI

Theodore A. Bass, MD, FSCAI, FACC
Medical Director, Cardiovascular Center
Professor of Medicine
University of Florida College of Medicine – Jacksonville Fl

SCAI Fellows Course
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Disclosures

Antiplatelet Therapy PCI:

Theodore A. Bass MD, FSCAI

The following relationships exist related to this presentation:

- Consulting: Lilly, Daiichi Sankyo  inactive 2 years
Basic Concepts
Thrombus Formation

Two key elements: **cellular** (platelets) and **plasmatic** (coagulation factors)

- Thrombin
- Platelet aggregation
- TXA₂
- ADP
- Fibrinogen → Fibrin
- Platelet activation
- ADP
- Collagen
- Tissue Factor
- Prothrombin
- Clotting cascade
- Plasma

THROMBUS
I. ANTIPLATELET DRUGS

• 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
Oral Antiplatelet Therapy in ACS/PCI

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?
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

(1st generation)

- P2Y₁₂ 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

Clopidogrel

(2nd generation)

- 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.).

Solution to these problems:
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.
# Adjunctive Clopidogrel Therapy in ACS/PCI

## UA/NSTEMI
- **CURE**
- 1 Year + Benefit
- *NEJM 2001*

## PCI
- **CREDO**
- 1 Year + Benefit
- *JAMA 2002*

## Acute STEMI
- **CLARITY**
- COMMIT (CCS-2)
- 30 Days + Benefit
- *NEJM 2005, Lancet 2005*
Strategies of ADP P2Y12 mediated platelet inhibition

[Diagram showing the mechanisms of direct acting and pro-drug inhibitors of ADP P2Y12 receptors, with pathways involving intracellular and extracellular signaling pathways, including Gs, Gi, Gq, cAMP, PDEIII, VASP, PKA, and P2X1 receptors.]

Angiolillo DJ et al. JACC Interv 2011
Healthy volunteer crossover study
IPA (20 μM ADP) at 24 hours

Response to clopidogrel 300 mg
Response to prasugrel 60 mg

Inhibition of platelet aggregation (%)

N=64

Brandt J et al. AHJ 2006
Balance of Efficacy and Safety

CV Death / MI / Stroke

Prasugrel

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

Clopidogrel

Prasugrel

TIMI Major
NonCABG Bleeds

Wiviott et al. NEJM 2007
ONSET/OFFSET Study

Loading Dose

Last Maintenance Dose

IPA %

0 10 20 30 40 50 60 70 80 90 100

0 .5 1 2 4 8 24 6 weeks 0 2 4 8 24 48 72 120 168 240

Onset Maintenance Offset

Time (hours)

Gurbel PA et al. Circulation 2010

Ticagrelor (n=54)
Clopidogrel (n=50)
Placebo (n=12)

20 µM ADP - Final Extent

*  

‡
K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)

<table>
<thead>
<tr>
<th>Days after randomisation</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9,333</td>
<td>9,291</td>
</tr>
<tr>
<td>60</td>
<td>8,628</td>
<td>8,521</td>
</tr>
<tr>
<td>120</td>
<td>8,460</td>
<td>8,362</td>
</tr>
<tr>
<td>180</td>
<td>8,219</td>
<td>8,124</td>
</tr>
<tr>
<td>240</td>
<td>6,743</td>
<td>6,743</td>
</tr>
<tr>
<td>300</td>
<td>5,161</td>
<td>5,096</td>
</tr>
<tr>
<td>360</td>
<td>4,147</td>
<td>4,047</td>
</tr>
</tbody>
</table>

HR 0.84 (95% CI 0.77–0.92), p=0.0003

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval
Non-CABG and CABG-related major bleeding

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (K-M estimated rate % per year)</th>
<th>Clopidogrel (K-M estimated rate % per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CABG PLATO major bleeding</td>
<td>4.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Non-CABG TIMI major bleeding</td>
<td>2.8</td>
<td>2.2</td>
</tr>
<tr>
<td>CABG PLATO major bleeding</td>
<td>7.4</td>
<td>7.9</td>
</tr>
<tr>
<td>CABG TIMI major bleeding</td>
<td>5.3</td>
<td>5.8</td>
</tr>
</tbody>
</table>

p=0.026
p=0.03
NS
NS
TRITON vs PLATO

Proof of concept: Higher IPA to Support ACS

Differences between trials

1. Patient Population
   - TRITON: ACS undergoing PCI (*indication only for ACS undergoing PCI*)
   - PLATO: Full spectrum ACS (*indication for ACS irrespective of management*)

2. Pretreatment
   - TRITON: No pretreatment (except STEMI)
   - PLATO: Pretreatment

3. Clopidogrel Loading Dose
   - TRITON: 300mg
   - PLATO: 300-600mg

4. Duration of trial (median)
   - TRITON: 14.5 months
   - PLATO: 9 months
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 (7 days).

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

  **Precautions:** compliance (b.i.d. administration), drug interactions (CYP 3A4 interfering agents ie antifungal, antiviral); regional differences (North America/ASA dose <100mg), COPD/asthma, bradyarrhythmia, gout syndromes, CABG/surgery (5 days).
1. Which drugs should we use?

2. When to start and at which dose?

3. Length of therapy?
Aspirin
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>Ischemic 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 (2P&lt;0.00001)</td>
</tr>
</tbody>
</table>

*BMJ 2002;324:71-86*
Aspirin Dose and Incidence of Major Bleedings

Insights from CURE

## ASA Dose Comparison

**Primary Outcome and Bleeding**

<table>
<thead>
<tr>
<th></th>
<th>ASA 75-100 mg</th>
<th>ASA 300-325 mg</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death/MI/Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI (2N=17,232)</td>
<td>4.2</td>
<td>4.1</td>
<td>0.98</td>
<td>0.84-1.13</td>
<td>0.76</td>
</tr>
<tr>
<td>No PCI (2N=7855)</td>
<td>4.7</td>
<td>4.4</td>
<td>0.92</td>
<td>0.75-1.14</td>
<td>0.44</td>
</tr>
<tr>
<td>Overall (2N=25,087)</td>
<td>4.4</td>
<td>4.2</td>
<td>0.96</td>
<td>0.85-1.08</td>
<td>0.47</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>2.1</td>
<td>1.9</td>
<td>0.91</td>
<td>0.73-1.12</td>
<td>0.37</td>
</tr>
<tr>
<td>TIMI Major Bleed</td>
<td>1.03</td>
<td>0.97</td>
<td>0.94</td>
<td>0.73-1.21</td>
<td>0.71</td>
</tr>
<tr>
<td>CURRENT Major Bleed</td>
<td>2.3</td>
<td>2.3</td>
<td>0.99</td>
<td>0.84-1.17</td>
<td>0.90</td>
</tr>
<tr>
<td>CURRENT Severe Bleed</td>
<td>1.7</td>
<td>1.7</td>
<td>1.00</td>
<td>0.83-1.21</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**GI Bleeds:** 30 (0.24%) vs 47 (0.38%), P=0.051

No other significant differences between ASA dose groups.
P2Y12 Inhibitors
A loading dose of a $\text{P}2\text{Y}_{12}$ receptor inhibitor should be given to patients undergoing PCI with stenting. Options include:

1. Clopidogrel 600 mg (ACS and non-ACS patients).
2. Prasugrel 60 mg (ACS patients).
3. Ticagrelor 180 mg (ACS patients).
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

ARMYDA-2 Trial: Primary endpoint

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

Clopidogrel pre-treatment 4-8 hrs before PCI

- 4% (n=126) for 600 mg
- 12% (n=129) for 300 mg

p = 0.041

Patti G et al. Circulation 2005
### Clopidogrel: Double vs Standard Dose
#### Primary Outcome and Components

<table>
<thead>
<tr>
<th>Event</th>
<th>Standard (2N=17,232)</th>
<th>Double (2N=17,232)</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
<th>Intn P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CV Death/MI/Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>4.5</td>
<td>3.9</td>
<td>0.85</td>
<td>0.74-0.99</td>
<td>0.036</td>
<td>0.016</td>
</tr>
<tr>
<td>No PCI</td>
<td>4.2</td>
<td>4.9</td>
<td>1.17</td>
<td>0.95-1.44</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>4.4</td>
<td>4.2</td>
<td>0.95</td>
<td>0.84-1.07</td>
<td>0.370</td>
<td></td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>2.6</td>
<td>2.0</td>
<td>0.78</td>
<td>0.64-0.95</td>
<td>0.012</td>
<td>0.025</td>
</tr>
<tr>
<td>No PCI</td>
<td>1.4</td>
<td>1.7</td>
<td>1.25</td>
<td>0.87-1.79</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2.2</td>
<td>1.9</td>
<td>0.86</td>
<td>0.73-1.03</td>
<td>0.097</td>
<td></td>
</tr>
<tr>
<td><strong>CV Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>1.9</td>
<td>1.9</td>
<td>0.96</td>
<td>0.77-1.19</td>
<td>0.68</td>
<td>1.0</td>
</tr>
<tr>
<td>No PCI</td>
<td>2.8</td>
<td>2.7</td>
<td>0.96</td>
<td>0.74-1.26</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2.2</td>
<td>2.1</td>
<td>0.96</td>
<td>0.81-1.14</td>
<td>0.628</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>0.4</td>
<td>0.4</td>
<td>0.88</td>
<td>0.55-1.41</td>
<td>0.59</td>
<td>0.50</td>
</tr>
<tr>
<td>No PCI</td>
<td>0.8</td>
<td>0.9</td>
<td>1.11</td>
<td>0.68-1.82</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.5</td>
<td>0.5</td>
<td>0.99</td>
<td>0.70-1.39</td>
<td>0.950</td>
<td></td>
</tr>
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</table>
**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 Better</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>
<tr>
<td>Overall CREDO Results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.5</td>
<td>0.23</td>
</tr>
</tbody>
</table>

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

Placebo

Clopidogrel

P = 0.020 for treatment / timing interaction

CURE: CABG-Related Bleeding

CURE Trial N Engl J Med 2001

% of Pts. Major Bleeding

- Clopidogrel + ASA
- ASA

<5 days

- %: 9.6
- % change: 53%
- P = 0.06
- N = 912

>5 days

- %: 6.3
- N = 910

- %: 4.4
- N = 910

- %: 5.3

P = NS
The loading dose of clopidogrel for patients undergoing PCI after fibrinolytic therapy should be 300 mg within 24 hours and 600 mg more than 24 hours after receiving fibrinolytic therapy.

Patients should be counseled on the need for and risks of DAPT before placement of intracoronary stents, especially a DES, and alternative therapies should be pursued if they are unwilling or unable to comply with the recommended duration of DAPT.
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.
PPIs and Antiplatelet Therapy

**PPI should be used in patients with history of prior GI 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.
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$_{12}$ inhibitor therapy after stent implantation should generally be as follows:

a) In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y$_{12}$ 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 P2Y$_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (e.g., >12 months) of P2Y$_{12}$ inhibitor therapy is reasonable.
Continuation of clopidogrel, prasugrel or ticagrelor beyond 12 months may be considered in patients undergoing DES placement.
Challenging the guidelines

One-year dual antiplatelet therapy is:

• Too long!

• Not long enough!
### What is the ‘Optimal’ Trial for the ‘Optimal’ DAPT Duration?

**DAPT durations, inclusion of BMS, landmarking and ‘event-free’ patients**

<table>
<thead>
<tr>
<th>Inclusion Group, N</th>
<th>DAPT Duration</th>
<th>DES Type</th>
<th>1° Endpoint</th>
<th>2° Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ISAR-SAFE</strong></td>
<td>6,000</td>
<td>6 vs 12 months</td>
<td>All DES</td>
<td>D/MI/Stroke/TIMI major bleed at 15 mos</td>
</tr>
<tr>
<td>6-month event free</td>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>REAL-LATE</strong></td>
<td>2,000</td>
<td>12 vs 24 months</td>
<td>All DES</td>
<td>2-yr Cardiac D/MI</td>
</tr>
<tr>
<td>12-month event free</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ZEST-LATE</strong></td>
<td>2,000</td>
<td>12 vs 24 months</td>
<td>SES, PES, ZES</td>
<td>2-yr D/MI</td>
</tr>
<tr>
<td>12-month event free</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OPTIMIZE</strong></td>
<td>3,120</td>
<td>3 vs. 12 months</td>
<td>Endeavor ZES</td>
<td>1-yr D/MI/Stroke/TIMI major bleed</td>
</tr>
<tr>
<td>non-STEMI</td>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SEASIDE</strong></td>
<td>900</td>
<td>6 months</td>
<td>Endeavor ZES</td>
<td>1-yr D/MI/Stroke</td>
</tr>
<tr>
<td>non-ACS</td>
<td></td>
<td></td>
<td></td>
<td>CYP2C19</td>
</tr>
</tbody>
</table>
How long do I continue clopidogrel therapy?

One-year in ALL of my ACS pts treated with DES!

I continue dual antiplatelet therapy for >1-year if:

The answer is “YES” to ANY of the below questions:

1) Multiple hospitalizations for ACS?
2) Broad atherosclerotic burden (i.e. PAD) or presence of DM?
3) Prior MI?

and the answer is “NO” to ANY of the below questions:

1) Prior bleeding?
2) Prior stroke?
3) Economic restraints?

In my stable CAD pts “I do not have a problem” with stopping clopidogrel at 6-months if treated with second generation DES, although “I still encourage” to comply with 12-months therapy.
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-class IIb C recommendation).
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.
Thank You