Antiplatelet Options After PCI: Managing the First Year

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Disclosures

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The following relationships exist related to this presentation

- None
Current Controversies on DAPT in PCI

- Which drug?
- When to start?
- Which dose?
- How long?
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

Hazard Ratio for ATP Discontinuation = 89

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.
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 P2Y₁₂ inhibitor therapy after stent implantation, earlier discontinuation (e.g., >12 months) of P2Y₁₂ inhibitor therapy is reasonable.
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>

*Bleeding*

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

Insights from CURE

RRR: 19%

AAS

AAS + Clopidogrel

<100 mg
n=5320
1.9%

100-200 mg
n=3109
2.8%

>200 mg
n=4110
3.7%

Minimum Duration of Clopidogrel Therapy in DES Pivotal Randomized Trials

- SIRIUS (Cypher): 3 months
- TAXUS IV (Taxus): 6 months
- ISAR-TEST (ISAR I DES): 6 months
- ENDEAVOR II (Endeavor): 3 months
- SPIRIT III (Xience): 6 months
- DIABETES I (Cypher): 12 months
- DIABETES II (Taxus): 12 months
DES and Prolonged DAPT

What are we treating?
The patient or the stent?
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).
A P2Y$_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.

- Ref #110: CURE
- Ref #130: TRITON
- Ref #132: PLATO

_Eur Heart J_ 2011; doi:10.1093/eurheartj/ehr236
NSTE-ACS: Evidence for Clopidogrel Use

CURE Primary Results (N=12,562)

Death, MI, or Stroke (%)

Placebo + ASA 11.4%

Clopidogrel + ASA 9.3%

20% RRR

P<0.001

Months of Follow Up

NSTE-ACS = non-ST segment elevation-acute coronary syndrome. RRR = relative risk ratio.

Risk-Adjusted Instantaneous Incidence Rates of Death or AMI Over Time After Stopping Treatment With Clopidogrel Among Medically Treated and PCI-Treated Patients With ACS Using Multivariable Cox Regression Models
Individual response variability to dual antiplatelet therapy

% Platelet aggregation (LTA-ADP 20μM)

Number of patients

Ischemic Risk
(including stent thrombosis)

Angiolillo DJ et al. Am J Cardiol 2006; 97: 38-43
TRITON TIMI 38
(prasugrel vs clopidogrel)

PLATO
(ticagrelor vs clopidogrel)
DES and Prolonged DAPT

In the setting of ACS (across the spectrum: UA, NSTEMI, STEMI) dual antiplatelet therapy with aspirin and a P2Y12 receptor inhibitor is the standard of care irrespective of management (medical therapy, percutaneous revascularization with POBA/BMS/DES, surgical revascularization).

Guideline recommendations since 2002 based on robust large scale clinical trial data. Little (or no) room to debate shorter duration of DAPT in DES treated patients in ACS.
Beyond 12 months?
CHARISMA – Prior MI

N = 3,846

- Placebo + ASA: 8.3%
- Clopidogrel + ASA: 6.6%

HR: 0.774 [95% CI: (0.613, 0.978)]
p = 0.031

Trial Schema

Stable pts with history of MI 1-3 yrs prior + ≥1 additional atherothrombosis risk factor*

N ~ 21,000

RANDOMIZE DOUBLE BLIND

Planned treatment with ASA 75 – 150 mg & Standard background care

Ticagrelor 90 mg bid

Ticagrelor 60 mg bid

Placebo

Follow-up Visits Q4 mos for 1st yr, then Q6 mos

Min 12 mos and median 26 mos follow-up Event-driven trial

Primary Efficacy Endpoint: CV Death, MI, or Stroke
Primary Safety Endpoint: TIMI Major Bleeding

*Age ≥65 yrs, diabetes, 2nd prior MI, multivessel CAD, or chronic non-end stage renal dysfunction
Dual Antiplatelet Therapy (DAPT) Study

- 50% of patients continue on dual antiplatelet therapy (clopidogrel or prasugrel)
- 50% of patients receive aspirin + placebo

Total 33-month patient evaluation including additional 3-month follow-up

DES
n=15,245

BMS
n=5400

All patients on aspirin + open-label thienopyridine therapy for 12 months

1:1 Randomization at month 12
Continuation of clopidogrel, prasugrel or ticagrelor beyond 12 months may be considered in patients undergoing DES placement.
Drawback of prolonged use: Bleeding!
PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia study

PRODIGY: Study Conclusions

Our study failed to show that prolonging DAPT for 24 months is superior to 6 month duration of Tx in pts receiving 1 or 2 gen DES or at least 1 month after BMS.

While we cannot rule out the possibility that a smaller than previously anticipated benefit may exist, the clear increase in bleeding, transfusion and net adverse clinical events, suggests that current recommendations may have overemphasized the benefit over the risk of long-term treatment with aspirin and clopidogrel.
Impact of MI and Major Bleeding (Non-CABG) in the First 30 Days on Risk of Death Over 1 Year

ACUITY

1 Year Estimate

- Both MI and Major Bleed (N=94) 28.9%
- Major Bleed Only (Without MI) (N=551) 12.5%
- MI Only (Without Major Bleed) (N=611) 8.6%
- No MI or Major Bleed (N=12,557) 3.4%

PPIs and Antiplatelet Therapy

PPI should be used in patients with history of prior GI who require DAPT.

PPI use is reasonable in patients with increased risk of gastrointestinal bleeding (advanced age, concomitant use of warfarin, steroids, nonsteroidal anti-inflammatory drugs, 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.
Challenging the guidelines

One-year dual antiplatelet therapy is:

- Too long!
- Not long enough!
### Stent-related efficacy and safety of early and new generation drug-eluting stents from randomised trials in unrestricted populations at 2 years

<table>
<thead>
<tr>
<th></th>
<th>Cypher sirolimus-eluting stent</th>
<th>Taxus paclitaxel-eluting stent</th>
<th>BioMatrix biolimus-eluting stent</th>
<th>Xience V everolimus-eluting stent</th>
<th>Resolute zotarolimus-eluting stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR at 2 years</td>
<td>7.1%</td>
<td>5.9%</td>
<td>6.3%</td>
<td>5.1%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Definite stent thrombosis at 2 years</td>
<td>2.5%</td>
<td>2.7%</td>
<td>2.2%</td>
<td>0.5%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

### Stent properties

<table>
<thead>
<tr>
<th>Stent</th>
<th>Strut Thickness</th>
<th>Polymer Thickness</th>
<th>Drug Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cypher</td>
<td>140 μm</td>
<td>2.5 μm</td>
<td>~10 ug/mm</td>
</tr>
<tr>
<td>Taxus Express</td>
<td>132 μm</td>
<td>2.7 μm</td>
<td>1 ug/mm²</td>
</tr>
<tr>
<td>Biomatrix</td>
<td>137 μm</td>
<td>2.2 μm</td>
<td>15.6 μg/mm</td>
</tr>
<tr>
<td>Endeavor</td>
<td>91 μm</td>
<td>1.3 μm</td>
<td>10 μg/mm</td>
</tr>
<tr>
<td>Xience V</td>
<td>81 μm</td>
<td>0.5 μm</td>
<td>~6 μg/mm</td>
</tr>
</tbody>
</table>

Data are from LEADERS, COMPARE, and RESOLUTE All Comers trials
Optimal Duration of Clopidogrel Therapy

**ISAR-SAFE**
A double-blind, placebo-controlled RCT

6000 DES Patients

6-month therapy

12-month therapy

Primary end point at 15 months
A composite of death, MI, stent thrombosis, stroke, major bleeding
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

- **Dual therapy**: 95.1%
- **Triple therapy (INR: 2.0-2.5)**: 66.7%
- **Triple therapy (INR > 2.5)**: 95.1%

† 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

*Note: Double underlining signifies emphasis on statistical significance.*
The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary stenting treated with clopidogrel

How long do I continue DAPT?

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 bellow 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 bellow 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.