CLOPIDOGRIL IS BETTER THAN PRASUGRIL IN PCI FOR NSTEMI

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Intensifying Platelet Inhibition
Navigating between Scylla and Charybdis

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EDITORIALS

Intensifying Platelet Inhibition — Navigating between Scylla and Charybdis
Deepak L. Bhatt, M.D.

In Greek mythology, Scylla was a ferocious beast and Charybdis was a monstrous whirlpool. The wily Odysseus successfully navigated between the two, but they caused marked increases in the risk of bleeding. Surprisingly, these oral agents did not reduce the risk of ischemic events and in fact were
Clinical trials of clopidogrel in real life

Plavix Robust Clinical Research Program

Published Trials


Publication Date

Most recent trials

ACTIVE ACTIVE

CREDO match CCS2

COMMIT CCS2

CHARISMA

CLARITY

Cure PCI-Cure

CARESS

CAPRIE

CLASSICS

Publication Date
### Clopidogrel studies in Cardiology

<table>
<thead>
<tr>
<th>Acute STEMI</th>
<th>NSTE ACS</th>
<th>PCI</th>
<th>Post MI</th>
<th>High risk of event</th>
</tr>
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#### Occluded Artery/D/MI
- 36% ↓

#### CVD/MI/UR:
- 20% ↓

#### Mortality
- 7% ↓
- Death, MI, or Stroke
- 9% ↓

#### D/MI/CVA
- up to 1 yr: 20% ↓
- up to 3 yrs: 8.7% ↓

#### D/MI/CVA
- up to 1 yr: 27% ↓

#### RRR: 7.7% ↓
- p=0.04

#### 2007 ESC guidelines on management of NSTE-ACS pts

For all patients, **immediate 300 mg** loading dose of Clopidogrel is recommended, followed by **75 mg** Clopidogrel daily (I-A). **Clopidogrel should be maintained for 12 months** unless there is an excessive risk of bleeding (I-A).
**STEMI patients***

>>> Plavix® should be added to aspirin in patients with STEMI regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy (I-A).

>>> Treatment with Plavix® should continue for at least 14 days (I-B) and it is reasonable to continue it for a period of 1 year (IIa-C).

>>> In patients less than 75 years old, who receive fibrinolytic therapy or who do not receive reperfusion therapy, it is reasonable to administer an oral loading dose of Plavix® 300 mg (IIa-C).
**TRITON – Study Design**

ACS patients (STEMI or UA/NSTEMI†) + planned PCI (n = 13,608)

Prasugrel

- 60 mg loading dose*

- 10 mg/day

Double-blind treatment: Minimum: 6 months; median = 14.5 months; maximum = 15 months

- ASA 75–162 mg/day

- Clopidogrel 75 mg/day (n = 6795)

Clopidogrel

- 300 mg loading dose*

Loading dose administered anytime after randomization until completion of the PCI procedure (within 1 hour after the patient leaves the catheterization lab). All decisions regarding concomitant medications are left to the treating physician.

†UA/NSTEMI patients had TIMI risk score >=3 and were within 72 hours of symptom onset

Adapted from Wiviott SD et al. Am Heart J 2006;152:627–635.

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**TRITON – 3 different patient subgroups**

UA/NSTEMI ≤ 72 h after symptom onset and TRS ≥ 3

STEMI 12 h – 14 d after symptom onset (post-STEMI)

STEMI ≤ 12 h after symptom onset (primary STEMI)

Diagnostic catheterization

- Medical Rx or CABG planned

- PCI planned

Do not randomize

Randomize (stratified by presenting syndrome)

Loading dose of study drug

PCI†

No PCI

Daily maintenance study drug + long-term follow-up

*TRS = TIMI risk score.†Adjunctive medical Rx and device selection at physician discretion.

TRITON: significant reduction in CV death, MI or stroke offset by significant increase in non-CABG TIMI major bleeding


TRITON: Consistent benefit of prasugrel versus clopidogrel in selected subgroups

TRITON: Timing of Loading Dose

Characteristics (%)  

<table>
<thead>
<tr>
<th>Prasugrel (n = 6,813)</th>
<th>Clopidogrel (n = 6,795)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

Timing of Study Drug Administration

| Before PCI | 26 | 25 |
| During PCI | 73 | 74 |
| After PCI  | 1  | 1  |

Definitions for loading dose timing:

- **Before PCI:** After randomization, but before the first coronary guidewire was placed.
- **During PCI:** After the first coronary guidewire was placed or within 1 hour after the patient was taken from the cardiac catheterization lab.
- **After PCI:** More than 1 hour after the patient was taken from the cardiac catheterization lab.


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TRITON: Significant increase with prasugrel in other bleeding categories in entire ACS cohort at 15 months

<table>
<thead>
<tr>
<th>Endpoint: N (%)</th>
<th>Prasugrel (n = 6,741)</th>
<th>Clopidogrel (n = 6,716)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI major or minor bleeding</td>
<td>303 (5.0)</td>
<td>231 (3.8)</td>
<td>1.31 (1.11–1.56)</td>
<td>0.002</td>
</tr>
<tr>
<td>Bleeding requiring transfusion</td>
<td>244 (4.0)</td>
<td>182 (3.0)</td>
<td>1.34 (1.11–1.63)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CABG-related TIMI major bleeding</td>
<td>24 (13.4)</td>
<td>6 (3.2)</td>
<td>4.73 (1.90–11.82)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Patients could have more than one type of event.

For major bleeding related to CABG, the total number of patients were all patients who had received at least one dose of prasugrel (n = 179) or clopidogrel (n = 189) before undergoing CABG. The ratio used for the CABG-related TIMI major bleeding endpoint was the odds ratio, not hazard ratio, and was evaluated with the use of the Cochran-Mantel-Haenszel test.

TRITON: Conclusions (1)

In patients with ACS and scheduled PCI

prasugrel therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis

In this population, prasugrel was also associated with an increased risk of major bleeding, including fatal bleeding

Overall mortality did not differ significantly between treatment groups


TRITON: Conclusions (2)

prasugrel is more effective at preventing ischemic events than with the inhibition by a standard regimen of clopidogrel.

However, this beneficial effect is accompanied by an increase in the rate of major bleeding.

When considering the choice of antiplatelet regimens for the treatment of patients with ACS who are undergoing PCI:

clinicians need to weigh the benefits and risks of intensive inhibition of platelet aggregation (real life scenarios).

Intensifying Platelet Inhibition — Navigating between Scylla and Charybdis

Deepak L. Bhatt, M.D.

In Greek mythology, Scylla was a fercous beast and Charybdis was a monstrous whirlpool. The wily Odysseus successfully navigated between them, but they caused marked increases in the risk of bleeding. Surprisingly, these oral agents did not reduce the risk of ischemic events and in fact were
17 CV death prevented vs 16 Fatal bleeding events caused
Summary

To minimize the risk of bleeding whilst preserving the benefit in terms of "prevention of atherothrombotic events", prasugrel has been approved in Europe:

- in a narrower population than that enrolled in TRITON (contraindicated in patients with previous stroke/TIA and "generally not recommended" in patients ≥ 75 years old)
- for a shorter duration of treatment (12 months) than the median duration of treatment studied in TRITON (14.5 month)
- at a lower maintenance dose (5mg) than that studied in TRITON for the sub-groups of patients at high risk of bleeding (patients ≥ 75 years old, < 60 kg body weight)

The safety profile of prasugrel is to be further investigated through a series of risk minimization activities required by the CHMP

CURRENT OASIS 7

CURRENT OASIS 7: A 2X2 Factorial Randomized Trial of Optimal Clopidogrel and Aspirin Dosing in Patients with ACS Undergoing an Early Invasive Strategy with Intent For PCI

Shamir R. Mehta on behalf of the CURRENT Investigators

Disclosures: CURRENT OASIS 7 was funded by a grant from sanofi-aventis and Bristol Myers Squibb. All data were managed independently of the sponsor at the PhRMA, McMaster University and the trial was overseen by an international steering committee of experts.
**Background**

**Clopidogrel**
- Clopidogrel 300 mg followed by 75 mg daily reduces major CV events across the spectrum of ACS and PCI
- Recent data suggest that **doubling** the loading and maintenance doses of clopidogrel results in a higher and more rapid antiplatelet effect

**Aspirin**
- Dose of ASA varies between Europe and North America
- No large-scale RCT’s have compared high (300-325 mg) versus low (75-100) dose aspirin in patients with ACS undergoing PCI

**Study Design, Flow and Compliance**

25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)
- Planned Early (<24 h) Invasive Management with intended PCI
- Ischemic ECG ∆ (80.8%) or ↑ cardiac biomarker (42%)

Randomized to receive (2 X 2 factorial):
- **CLOPIDOGREL**: Double-dose (600 mg then 150 mg/d x 7 d then 75 mg/d) vs Standard dose (300 mg then 75 mg/d)
- **ASA**: High Dose (300-325 mg/d) vs Low dose (75-100 mg/d)

- **PCI**: 17,232 (70%)
- **Angio**: 24,769 (99%)
- **No PCI**: 7,855 (30%)

- No Sig. CAD 3,616
- CABG 1,809
- CAD 2,430

Clop in 1st 7d (median) 7d
- 7 d
- 2 d
- 7d

**Efficacy Outcomes**: CV Death, MI or stroke at day 30
- Stent Thrombosis at day 30

**Safety Outcomes**: Bleeding (CURRENT defined Major/Severe and TIMI Major)

**Key Subgroup**: PCI v No PCI

Complete Followup 99.8%
Clopidogrel: Double vs Standard Dose
Definite Stent Thrombosis (Angio confirmed)

Cumulative Hazard

0.0 0.004 0.008 0.012
0 3 6 9 12 15 18 21 24 27 30 Days

Clopidogrel Standard Dose
Clopidogrel Double Dose

42% RRR

HR 0.58
95% CI 0.42-0.79
P=0.001

Clopidogrel: Double vs Standard Dose
Major Efficacy Outcomes in PCI Patients

<table>
<thead>
<tr>
<th>Day 30</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard</td>
</tr>
<tr>
<td></td>
<td>N=8684</td>
</tr>
<tr>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>2.3</td>
</tr>
<tr>
<td>Definite</td>
<td>1.2</td>
</tr>
<tr>
<td>MI</td>
<td>2.6</td>
</tr>
<tr>
<td>MI or stent thrombosis</td>
<td>3.7</td>
</tr>
<tr>
<td>CV Death</td>
<td>1.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.4</td>
</tr>
<tr>
<td>CV Death/MI/Stroke</td>
<td>4.5</td>
</tr>
</tbody>
</table>
**Clopidogrel Double vs Standard Dose Bleeding PCI Population**

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard</td>
<td>Double</td>
<td>Hazard</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>N= 8684</td>
<td>N=8548</td>
<td></td>
<td>Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI Major¹</td>
<td>0.5</td>
<td>0.5</td>
<td>1.06</td>
<td>0.70-1.61</td>
<td>0.79</td>
</tr>
<tr>
<td>CURRENT Major²</td>
<td>1.1</td>
<td>1.6</td>
<td>1.44</td>
<td>1.11-1.86</td>
<td>0.006</td>
</tr>
<tr>
<td>CURRENT Severe³</td>
<td>0.8</td>
<td>1.1</td>
<td>1.39</td>
<td>1.02-1.90</td>
<td>0.034</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.15</td>
<td>0.07</td>
<td>0.47</td>
<td>0.18-1.23</td>
<td>0.125</td>
</tr>
<tr>
<td>ICH</td>
<td>0.035</td>
<td>0.046</td>
<td>1.35</td>
<td>0.30-6.04</td>
<td>0.69</td>
</tr>
<tr>
<td>RBC transfusion ≥ 2U</td>
<td>0.91</td>
<td>1.35</td>
<td>1.49</td>
<td>1.11-1.98</td>
<td>0.007</td>
</tr>
<tr>
<td>CABG-related Major</td>
<td>0.1</td>
<td>0.1</td>
<td>1.69</td>
<td>0.61-4.7</td>
<td>0.31</td>
</tr>
</tbody>
</table>

¹ICH, Hb drop ≥ 5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal
²Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units
³Fatal or Hb ≥ 5 g/dL, sig hypotension + inotropes/surgery, ICH or tran of ≥ 4 units

**Conclusions**

**Clopidogrel Dose Comparison**

1. Double-dose clopidogrel significantly reduced stent thrombosis and major CV events (CV death, MI or stroke) in PCI.

2. In patients not undergoing PCI, double dose clopidogrel was not significantly different from standard dose (70% had no significant CAD or stopped study drug early for CABG).

3. There was a modest excess in CURRENT-defined major bleeds but no difference in TIMI major bleeds, ICH, fatal bleeds or CABG-related bleeds.
Conclusions
ASA Dose Comparison

No significant difference in efficacy or bleeding between ASA 300-325 mg and ASA 75-100 mg.

Comparison of CURRENT and TRITON

<table>
<thead>
<tr>
<th></th>
<th>CURRENT PCI (N=17,232)</th>
<th>TRITON (N=13,608)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death, MI or Stroke</td>
<td>↓ 15%</td>
<td>↓ 19%</td>
</tr>
<tr>
<td></td>
<td>↓ 21% (w high dose ASA)</td>
<td></td>
</tr>
<tr>
<td>Definite Stent Thrombosis</td>
<td>↓ 42%</td>
<td>↓ 58%</td>
</tr>
<tr>
<td></td>
<td>↓ 51% (w high dose ASA)</td>
<td></td>
</tr>
<tr>
<td>TIMI Major Bleed</td>
<td>No increase</td>
<td>↓ 32%</td>
</tr>
<tr>
<td>CABG-related Bleeding</td>
<td>No increase</td>
<td>↑ 4-fold</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>No increase</td>
<td>↑ 4-fold</td>
</tr>
</tbody>
</table>
Clinical Implications

1. For every 1,000 patients with ACS receiving PCI, using double-dose clopidogrel for 7 days instead of standard dose will prevent an additional 6 MI’s and 7 stent thromboses with an excess of 3 severe bleeds and no increase in fatal, CABG-related or TIMI major bleeds.

2. Patients not undergoing PCI should continue to use the standard dose regimen of clopidogrel.

In non STEMI patients going for PCI should I use PRASUGREL

• With most benefit in STEMI

• Lack of consistency of benefit in certain subsets of patients (> 75 years, previous strokes or TIA’s, those less than 60 Kg (> nonfatal and fatal stroke).

• Concerns about the > incidence of cancer.

• No phase 3 trials to endorse safety of 5 mg in high risk patients
• High risk of bleeding if CABG is an emergency Very.
• No known benefit if medical therapy is contemplated.
In non STEMI patients planned for PCI should I use CLOPIDOGREL

• With slightly lower benefit in non STEMI (TRITON) (no preloading in 75% of patients and only 300 mgs)

• Consistency of benefit in all subsets of patients (≥ 75 years, previous strokes or TIA, those less than 60 Kg)

• No concerns about the > incidence of cancer.

• Doubling loading does and maintenance for 7 days

>>> similar outcome in all ACS pts planned for PCI with modest risk of > non fatal bleeding.

• Lower risk of bleeding if CABG is an emergency

• Proven benefit if medical therapy is contemplated.