Clopidogrel Use in ACS and PCI: Clinical Trial Update

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PCI-CURE: *Clopidogrel vs placebo + aspirin in patients with ACS undergoing PCI*

Composite of MI or cardiovascular death from randomization to end of follow-up

- Placebo + ASA: 12.6%
- Clopidogrel + ASA: 8.8%

31% RRR

OASIS 7 - CURRENT
Randomizing patients to low vs. high-dose clop + ASA

25,807 ACS patients
Intended PCI < 24 hrs
No restriction on GP IIb/IIIa inhibitors

- Clopidogrel 600 mg
  - 150 mg from Day 2 to Day 7
  - 75 mg from Day 8 to 30

- Clopidogrel 300 mg
  - 75 mg from Day 2 to 30

- ASA 300 mg Day 1
  - 75–100 mg from Day 2 to 30

- ASA 300 mg Day 1
  - 300 mg–325 mg from Day 2 to 30

ClinicalTrials.gov Identifier: NCT00335452.
# Clopidogrel: Double vs Standard Dose

## Primary Outcome and Components

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Double</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 (2N=17,232)</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 (2N=7855)</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 (2N=25,087)</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 (2N=17,232)</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 (2N=7855)</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 (2N=25,087)</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>
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<tr>
<td><strong>CV Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI (2N=17,232)</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 (2N=7855)</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 (2N=25,087)</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 (2N=17,232)</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>
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<tr>
<td>No PCI (2N=7855)</td>
<td>0.8</td>
<td>0.9</td>
<td>1.11</td>
<td>0.68-1.82</td>
<td>0.67</td>
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<tr>
<td>Overall (2N=25,087)</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>
</tbody>
</table>
## Clopidogrel Double vs Standard Dose
### Bleeding Overall Population

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard N=12579</td>
<td>Double N=12508</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI Major¹</td>
<td>0.95</td>
<td>1.04</td>
<td>1.09</td>
<td>0.85-1.40</td>
</tr>
<tr>
<td>CURRENT Major²</td>
<td>2.0</td>
<td>2.5</td>
<td>1.25</td>
<td>1.05-1.47</td>
</tr>
<tr>
<td>CURRENT Severe³</td>
<td>1.5</td>
<td>1.9</td>
<td>1.23</td>
<td>1.02-1.49</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.11</td>
<td>0.13</td>
<td>1.15</td>
<td>0.56-2.35</td>
</tr>
<tr>
<td>ICH</td>
<td>0.05</td>
<td>0.03</td>
<td>0.67</td>
<td>0.19-2.37</td>
</tr>
<tr>
<td>RBC transfusion ≥ 2U</td>
<td>1.76</td>
<td>2.21</td>
<td>1.26</td>
<td>1.06-1.51</td>
</tr>
<tr>
<td>CABG-related Major</td>
<td>0.9</td>
<td>1.0</td>
<td>1.10</td>
<td>0.85-1.42</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 txn of ≥ 4 units
PRINCIPLE TIMI-44:
Comparative Pharmacodynamics of Prasugrel and High-Dose Clopidogrel

IPA (20 mM ADP)

N = 201  P<0.0001 for each

Prasugrel 60 mg

Clopidogrel 600 mg

Could just move this up to before TRITON RESULTS.
TRITON-TIMI 38: Balance of Efficacy and Safety

- **CV Death/MI/Stroke**: Prasugrel (HR 0.81, 95% CI, 0.73–0.90) vs. Clopidogrel (HR 0.79, 95% CI, 0.69–0.89), P<0.001)
- **TIMI Major Non-CABG Bleeds**: Prasugrel (HR 1.32, 95% CI, 1.03–1.68) vs. Clopidogrel (HR 0.52, 95% CI, 0.37–0.74), P=0.03

NNT=46
NNH=167

ADP-induced Platelet Reactivity on Clopidogrel Therapy Varies Widely Among Individuals

The Generation of Clopidogrel’s Active Metabolite is Inefficient and CYP450-Dependent

Association of Cytochrome P450 2C19 Genotype With the Antiplatelet Effect and Clinical Efficacy of Clopidogrel Therapy

429 Healthy Amish after Clopidogrel 75 mg X 7d

$CYP2C18-CYP2C19-CYP2C9-CYP2C8$ cluster

$P = 1.5 \times 10^{-13}$
Influence of CYP2C19*2 In Clopidogrel-Treated Patients

TRITON Results According to Carriage of Reduced Function CYP2C19 Allele

12.1%

Carriers

P = 0.01

8.0%

Non-carriers

Reduced function allele present in 30% of population

**CYP2C19 and MACE: A Collaborative Meta-analysis**

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Carriers vs Non-Carriers</td>
<td>1.61 (1.28-2.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heterozygotes vs Wildtype</td>
<td>1.50 (1.08-2.08)</td>
<td>0.016</td>
</tr>
<tr>
<td>Homozygotes vs Wildtype</td>
<td>1.81 (1.21-2.71)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

N=9,684

Mega JL et al, AHA 2009
**CYP2C19 and Stent Thrombosis: A Collaborative Meta-analysis**

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<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
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</thead>
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<tr>
<td>Carriers vs Non-Carriers</td>
<td>2.76 (1.77-4.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heterozygotes vs Wildtype</td>
<td>2.51 (1.59-3.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Homozygotes vs Wildtype</td>
<td>4.78 (2.01-11.39)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Risk Higher with CYP2C19 Variant
Risk Lower with CYP2C19 Variant

N=5,772

Mega JL et al, AHA 2009
Out-of-hospital 6-Month Outcomes Post-PCI Stratified by Reactivity in Patients on Consistent Clopidogrel Therapy at 6 Months

*On clopidogrel at 30 day & 6-month FU or reached an endpoint on clopidogrel by 6-month FU

**Standard Therapy**
placebo loading dose, then clopidogrel 75mg +placebo/day

**Tailored Therapy**
clopidogrel 600-mg*, then clopidogrel 150-mg/day

Successful PCI with DES without major complication or GPIIb/IIIa use

VerifyNow P2Y12 Assay 12-24 hours post-PCI

Yes

**PRU ≥ 230?**

High On-treatment Reactivity

A

N = 1100

“Tailored Therapy”
clopidogrel 600-mg*, then clopidogrel 150-mg/day

No

Normal On-treatment Reactivity

Random Selection

B

N = 1100

“Standard Therapy”
placebo loading dose, then clopidogrel 75mg +placebo/day

C

N = 583

“Standard Therapy”
placebo loading dose
clopidogrel 75mg +placebo/day

Clinical Follow-up And Platelet Function Assessment at 30 days, 6M

**Primary Endpoint:** 6 month CV Death, Non-Fatal MI, ARC definite/prob ST

**Safety Endpoint:** GUSTO Moderate or Severe Bleeding

*total first day dose

Price MJ et al, Am Heart J 2009
The Degree of CYP2C19 Inhibition Differs Among The Proton Pump Inhibitors

Ki (μM)

Rabeprazole (Aciphex)
Pantoprazole (Protonix)
Lansoprazole (Prevacid)
Esomeprazole (Nexium)
Omeprazole (Prilosec)

Ki = concentration required to decrease metabolic activity by 50%

Li XQ et al, Drug Metab Dispos 2004;32(8):821-7

SCRIPPS CLINIC
Omeprazole CLopidogrel Aspirin (OCLA) Study:
A randomized, placebo controlled trial of the influence of omeprazole on the PD effect of clopidogrel

Lower PRI means greater platelet inhibitory effect

N=120 (60 each group)

Influence of PPI Therapy on Outcome After ACS in Clopidogrel Treated Patients – A Retrospective Analysis

Ho et al, JAMA. 2009;301(9):937-944.
TRITON: Primary endpoint stratified by use of a PPI

PPI use at randomization (n= 4529)

- No PPI
- PPI

**CLOPIDOGREL**
- PPI vs no PPI: Adj HR 0.94, 95% CI 0.80-1.11

**PRASUGREL**
- PPI vs no PPI: Adj HR 1.00, 95% CI 0.84-1.20

Survival Curves for PPI Treated vs Placebo
Composite GI Events

HR = 0.55
95% CI = 0.36; 0.85
p=0.007
(preliminary)

Placebo: 67 events, 1895 at risk
Treated: 38 events, 1878 at risk
No PPI-clopidogrel interaction, or a net null effect? Interference with clop effect balanced by Prevention of events that precipitate DAPT d/c?

HR = 1.02
95% CI = 0.70; 1.51

Adjustment through Cox Proportional Hazards Model Adjusted to Positive NSAID Use and Positive H. Pylori Status
**FAMOUS:** Famotidine 20-mg Bid for the Prevention of Esophagitis in Patients Taking Low-Dose Aspirin

Incidence of peptic ulcers

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n=200)</th>
<th>Famotidine (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>14.5%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Peptic ulcers</td>
<td>4.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Duodenal</td>
<td>8.0%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

- P = 0.0002

Grades of erosive esophagitis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Placebo (n=200)</th>
<th>Famotidine (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td>A</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>B</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>C</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>D</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- P < 0.0001

_Taha et al, Lancet 2009;374:119-25_
Summary

• CURRENT-OASIS 7: no ischemic benefit of short course of high-dose clopidogrel in ACS patients undergoing an invasive management strategy, with higher rates of major bleeding.
  – Sub-group analysis of the PCI population appears to show ischemic benefit with high-dose therapy.

• Carriage of a CYP2C19 loss-of-function allele, which decreases clopidogrel AM generation and reduces its antiplatelet effect, has been associated with MACE in TRITON and in other trials.
  – Homozygosity (poor metabolizers substantially higher risk)
Summary (2)

- CYP2C19 genotype explains only a portion of the variability of clopidogrel’s antiplatelet effect.

- Randomized trials of “tailored” antiplatelet therapy based on platelet function testing (phenotype), such as GRAVITAS, are ongoing.

- The “PPI story” is still not finished. If GI treatment is necessary, consider pantoprazole, rabeprazole, or, famotidine.