Double-Dose Clopidogrel in ACS:
The CURRENT/OASIS-7 Trial

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Among patients with ACS, clopidogrel 300mg followed by 75 mg/d maintenance dose has been shown to improve short and long-term outcomes compared with ASA alone.

Many patients do not achieve sufficient platelet inhibition with standard dose clopidogrel.

Recent studies have shown that higher doses of clopidogrel lead to more rapid and higher levels of platelet inhibition.

Whether these pharmacodynamic findings translate into improved clinical outcomes is less certain.
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 $\Delta$ (80.8%) or $\uparrow$ cardiac biomarker (42%)

Randomized to receive (2 X 2 factorial):
- CLOPIDOGREL: **Double-dose** (600 mg then 150 mg/d x 7d 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 7d 2d 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 vs No PCI

Complete Followup 99.8%
# ASA Dose Comparison

Primary Outcome and Bleeding

<table>
<thead>
<tr>
<th>Outcome</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>4.2</td>
<td>4.1</td>
<td>0.98</td>
<td>0.84-1.13</td>
<td>0.76</td>
</tr>
<tr>
<td>PCI (2N=17,232)</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>No PCI (2N=7855)</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>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%) v 47 (0.38%), P=0.051

No other significant differences between ASA dose groups
2 Significant Interactions:

1. PCI v No PCI (P=0.016)
2. ASA dose (P=0.043)
Clopidogrel Dose vs. ASA Dose
Clopidogrel Double-Dose vs. Single-Dose by ASA Factorial

P int = 0.043

P=0.036

P=0.42

P=0.37
ASA Dose Interaction: Is it real?

- Interaction statistically borderline (p=0.043)
- No biologic plausibility
- If there were an ASA interaction, might expect the benefit of clopidogrel would be greater in low-dose ASA but the opposite was observed
- If there were a true ASA interaction, would expect the interaction would be accentuated for the most platelet-specific endpoint (stent thrombosis) not seen in CURRENT
Definite Stent Thrombosis According to Clopidogrel and ASA Dose

<table>
<thead>
<tr>
<th></th>
<th>Standard Clop</th>
<th>Double Clop</th>
<th>HR</th>
<th>P</th>
<th>P Int^n</th>
</tr>
</thead>
<tbody>
<tr>
<td>High ASA</td>
<td>1.2</td>
<td>0.6</td>
<td>0.49</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Low ASA</td>
<td>1.2</td>
<td>0.8</td>
<td>0.6</td>
<td>0.058</td>
<td>0.35</td>
</tr>
</tbody>
</table>
ASA Dose Interaction: Is it real?

Conclusions
• C vs. A interaction unlikely to be real

Implication
• Don’t need to analyze clopidogrel dose separately by ASA dose
Clopidogrel Dose vs. PCI Strategy
Clopidogrel Double- vs. Single-Dose by PCI Attempted

\[ P_{int} = 0.016 \]

- **PCI**
  - Std. Dose: 4.5%
  - Double Dose: 3.9%
  - \( P = 0.036 \)

- **No PCI**
  - Std. Dose: 4.9%
  - Double Dose: 4.2%
  - \( P = 0.14 \)

- **Overall**
  - Std. Dose: 4.4%
  - Double Dose: 4.2%
  - \( P = 0.37 \)
PCI-Clodidogrel Dose Interaction: Is it real?

• Statistical interaction fairly strong (p=0.016)

Previous studies consistently demonstrate a true effect.

Conclusions
• C vs. PCI interaction is most likely a true effect

Implication
• Need to analyze clopidogrel dose separately by PCI strategy

• Benefits of high-dose vs. low dose clopidogrel on biomarker release previously shown in PCI patients (ARMYDA-2 trial)
PCI Population
(N = 17,232)
# Clopidogrel: Double vs Standard Dose
## Major Efficacy Outcomes in PCI Patients

<table>
<thead>
<tr>
<th>Day 30</th>
<th>Clopidogrel Standard N=8684 %</th>
<th>Double Dose N=8548 %</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent Thrombosis</td>
<td>2.3</td>
<td>1.6</td>
<td>0.71</td>
<td>0.57-0.89</td>
<td>0.002</td>
</tr>
<tr>
<td>Definite</td>
<td>1.2</td>
<td>0.7</td>
<td>0.58</td>
<td>0.42-0.79</td>
<td>0.001</td>
</tr>
<tr>
<td>MI</td>
<td>2.6</td>
<td>2.0</td>
<td>0.78</td>
<td>0.64-0.95</td>
<td>0.012</td>
</tr>
<tr>
<td>MI or stent thrombosis</td>
<td>3.7</td>
<td>3.0</td>
<td>0.80</td>
<td>0.68-0.94</td>
<td>0.008</td>
</tr>
<tr>
<td>CV Death</td>
<td>1.9</td>
<td>1.9</td>
<td>0.96</td>
<td>0.77-1.19</td>
<td>0.68</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.4</td>
<td>0.4</td>
<td>0.88</td>
<td>0.55-1.41</td>
<td>0.59</td>
</tr>
<tr>
<td>CV Death/MI/Stroke</td>
<td>4.5</td>
<td>3.9</td>
<td>0.85</td>
<td>0.74-0.99</td>
<td>0.036</td>
</tr>
</tbody>
</table>
Clopidogrel: Double vs Standard Dose

Primary Outcome: PCI Patients

Clopidogrel Standard

Clopidogrel Double

HR 0.85
95% CI 0.74-0.99
P=0.036

15% RRR
Clopidogrel: Double vs Standard Dose
Definite Stent Thrombosis

HR 0.58
95% CI 0.42-0.79
P=0.001
PCI Subgroup: Definite Stent Thrombosis According to Stent Type

**Bare Metal Stents**

- Clopidogrel Standard Dose
- Clopidogrel Double Dose

HR 0.63
95% CI 0.43-0.94
P=0.024

**Drug-Eluting Stents**

- Clopidogrel Standard Dose
- Clopidogrel Double Dose

HR 0.50
95% CI 0.30-0.85
P=0.01

37% RRR
50% RRR
## Clopidogrel Double vs Standard Dose Bleeding PCI Population

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard</td>
<td>Double</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N= 8684</td>
<td>N=8548</td>
<td></td>
<td></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 txn of ≥ 4 units
1. Double-dose clopidogrel significantly reduced stent thrombosis and major CV events (CV death, MI or stroke) in patients undergoing 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.
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.