Optimal **Duration** and **Dose** of Antiplatelet Therapy after PCI

Donghoon Choi, MD, PhD
Severance Cardiovascular Center
Yonsei University College of Medicine
Optimal Duration of Antiplatelet Therapy after PCI
For all post-PCI stented patients receiving a DES, clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding.

For post-PCI patients receiving a BMS, 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).
Continuation of clopidogrel therapy beyond 1 year may be considered in patients undergoing DES placement.

(New Recommendation)
Contents

1. Clinical Data of long term use in dual anti-platelet therapy
   - Controversial
   - Supporting

2. Answers from on-going trials for long term use?
Contents

1. Clinical Data of long term use in dual anti-platelet therapy
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Discontinuation of Thienopyridine and Risk of Stent Thrombosis: Milan-Siegburg Cohort Study

3,021 patients with 5,389 lesions treated with DES (2002-2004)

Discontinuation of Thienopyridine and Risk of Stent Thrombosis With Sirolimus-Eluting Stents

Landmark Analysis on Thienopyridine Use Beyond 6 Months

Duration of Dual Antiplatelet Therapy after Implantation of Drug-Eluting Stents

ZEST-LATE

N=1,357
Patients who had participated in ZEST trial

REAL-LATE

N=1,625
Broader population of patients who had received any DES

N=2,701
Patients who were free of MACCE with dual antiplatelet therapy for at least a 12 month after DES implantation

Randomization

N=1,344
Aspirin Alone

N=1,357
Clopidogrel +Aspirin

2-Year F/U
- Clinical follow-up every 6 months
- Composite of MI or Death from cardiac causes

From July 2007 through September 2008

Park SJ et al. NEJM 2010
Primary End Point: Cardiac Death or Myocardial Infarction

[A graph showing the cumulative incidence of myocardial infarction (MI) or death from cardiac causes. The graph compares the effects of aspirin alone, clopidogrel + aspirin, and the differences in cumulative incidence over time.]

No. at Risk
- Clopidogrel + aspirin: 1357, 1122, 299
- Aspirin alone: 1344, 1100, 301

P = 0.17
Definite Stent Thrombosis

No. at Risk

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<tr>
<th>Group</th>
<th>Continuation</th>
<th>Discontinuation</th>
<th>Total</th>
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<td>301</td>
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<td>Discontinuation group</td>
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<td>1102</td>
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Park SJ et al. NEJM 2010
1. Clinical Data of long term use in dual anti-platelet therapy
   - Controversial
   - Supporting
2. Answers from on-going trials for long term use?
CREDO: Study Design

**Clopidogrel Arm**
- Pretreatment (3-24 h before PCI)
  - Clopidogrel 300 mg + ASA† (325 mg)

**Placebo Arm**
- Placebo + ASA† (325 mg)

PCI
- Clopidogrel 75 mg QD + ASA† (325 mg QD)
- Placebo QD + ASA† (81-325 mg) QD

28 Days
- Clopidogrel 75 mg QD
- Placebo QD + ASA† (81-325 mg) QD

12 Months
- Clopidogrel 75 mg QD
- Placebo QD + ASA† (81-325 mg) QD

† Plus other standard therapies

CREDO: Long-Term Benefits of Clopidogrel in PCI Patients

MI, Stroke, or Death – ITT Population

CREDO: Overall Safety of DAT at 1 Year

- Major bleeding at 1 year (p=0.07)
  - 8.8% clopidogrel
  - 6.7% placebo
- Minor bleedings rates were comparable (p=0.84)
  - 5.3% clopidogrel
  - 5.6% placebo
- No fatal bleeds or intracranial hemorrhages

Benefits of Long-term DAT

1. ‘CAPRIE-like subgroup’ in CHARISMA
   DAT for 30 months is better than ASA monotherapy

2. Duke Registry
   DAT > 6 months or 12 months is better than DAT<6 months

3. Denver, Seattle, Durham, & Richmond Network Data
   DAT > 6 months is better than DAT <6 months

4. European data
   DAT> 1 year is better than DAT < 1 year
‘CAPRIE like’ CHARISMA in Patients With Previous MI, IS, or PAD (Post hoc analysis)

Primary Outcome Event Rate (%)

N=9,478

Placebo + ASA

Clopidogrel + ASA

Primary Endpoint (MI/Stroke/CV Death)

RRR: 17.1 % (95% CI: 4.4%, 28.1%)
P=0.01

Adjusted Cumulative Mortality and MI Rates

Using the 6-Month Landmark Analysis

## Adjusted Cumulative Mortality and MI Rates

Using the **12-Month Landmark Analysis**

### Mortality

<table>
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<tr>
<th>No. at Risk</th>
<th>Months</th>
<th>DES w/ Clopidogrel</th>
<th>252</th>
<th>237</th>
<th>230</th>
<th>252</th>
<th>237</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>w/o Clopidogrel</td>
<td>276</td>
<td>258</td>
<td>244</td>
<td>276</td>
<td>256</td>
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<tr>
<td>BMS</td>
<td></td>
<td>w/ Clopidogrel</td>
<td>346</td>
<td>339</td>
<td>331</td>
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<td>w/o Clopidogrel</td>
<td>1644</td>
<td>1627</td>
<td>1596</td>
<td>1644</td>
<td>1621</td>
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</table>

### Composite of Death or MI

<table>
<thead>
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<th>No. at Risk</th>
<th>Months</th>
<th>DES w/ Clopidogrel</th>
<th>252</th>
<th>237</th>
<th>230</th>
<th>252</th>
<th>237</th>
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<tbody>
<tr>
<td></td>
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<td>w/o Clopidogrel</td>
<td>276</td>
<td>258</td>
<td>244</td>
<td>276</td>
<td>256</td>
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<tr>
<td>BMS</td>
<td></td>
<td>w/ Clopidogrel</td>
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<td>331</td>
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<td></td>
<td></td>
<td>w/o Clopidogrel</td>
<td>1644</td>
<td>1627</td>
<td>1596</td>
<td>1644</td>
<td>1621</td>
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</tbody>
</table>

Clopidogrel and Long-Term Outcomes after Stent Implantation for Acute Coronary Syndrome

Cumulative all-cause mortality between patients continuing and discontinuing clopidogrel

Ho PM et al. *AHJ* 2007
Comparison of the Impact of Short (<1 Year) and Long-Term (≥ 1 year) Clopidogrel Use Following PCI on Mortality

- The use of clopidogrel for ≥ 1 year after PCI was associated with lower Mortality.

Brar et al. J Am Coll Cardiol 2008; 51:2220-7
Contents

1. Clinical Data of long term use in dual anti-platelet therapy
   - Controversial
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2. Answers from on-going trials for long term use?
Answer of the optimal duration of DAT from on-going Trials

1. ISAR-SAFE (Germany)
2. OPTIMIZE (Brazil)
3. DAPT Trial (USA)
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

ISAR-SAFE

Drug-Eluting Stenting

Continuous Clopidogrel therapy for 5 to 8 months

Randomization

Placebo for 6 months

Clopidogrel 75 mg/d for 6 months

Follow Up

1st FU: 1 month after randomization

2nd FU: 6 months after randomization (at least one day after study drug cessation)

3rd FU: 9 months after randomization (at least 3 months after study drug cessation)

OPTIMIZE Randomized Trial

3,120 patients undergoing PCI with *Endeavor®* DES in ~30 clinical sites in Brazil

Randomization 1:1

October/2009

Short-term DAPT
3-month
N=1,560

Long-term DAPT
12-month
N=1,560

Clinical follow-up 1, 3, 6 and 12 months, and annually up to 3 years
Dual Antiplatelet Therapy (DAPT) Study

All patients on aspirin + open-label thienopyridine therapy for 12 months (1:1 Randomization at Month 12)

- DES (n = 15,245)
- BMS (n = 5,400)

12 months

18 months

50% patients continue on DAT

50% patients receive aspirin + placebo

Total 33 month patient evaluation including additional 3-month follow-up
Optimal duration of DAT

1. Several on-going studies may give us the answers to questions that “long term DAT would be clinically better than short term DAT?”

2. It might be too early to say that 1 year of DAT is enough for all patients post-PCI till we have more evidence.

3. Patient-based approach would be ideal!

   “Long-term DAT would be reasonable for high risk patients with previous ST, AMI, DM, and Bifurcation multi-stenting.”
Optimal Dose of Antiplatelet Therapy after PCI
Primary Results of The Gauging Responsiveness with A VerifyNow Assay - Impact on Thrombosis And Safety Trial

GRAVITAS
AHA 2010

Matthew J. Price, MD
On behalf of the GRAVITAS Investigators
**GRAVITAS Study Design**

Elective or Urgent PCI with DES*

VerifyNow P2Y12 Test 12-24 hours post-PCI

PRU ≥ 230

- **High-Dose Clopidogrel**:
  - clopidogrel 600-mg, then
  - clopidogrel 150-mg daily X 6 months

- **Standard-Dose Clopidogrel**:
  - clopidogrel 75-mg daily X 6 months

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**Primary Efficacy Endpoint:** CV Death, Non-Fatal MI, Stent Thrombosis at 6 mo

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

**Pharmacodynamics:** Repeat VerifyNow P2Y12 at 1 and 6 months

*Peri-PCI clopidogrel per protocol-mandated criteria to ensure steady-state at 12-24 hrs

†placebo-controlled  All patients received aspirin (81-162mg daily)
5429 patients screened with VerifyNow P2Y12 12-24 hours post-PCI

2214 (41%) with high residual platelet reactivity (PRU ≥ 230)

3215 (59%) without high residual platelet reactivity (PRU < 230)

Clopidogrel High Dose N=1109

Clopidogrel Standard Dose N=1105
Primary Endpoint: CV Death, MI, Stent Thrombosis

2.3% vs. 2.3%
HR 1.01 (95% CI 0.58 - 1.76)
p=0.98

Observed event rates are listed; P value by log rank test.
Bleeding Events: Safety Population

Severe or life-threatening: Fatal bleeding, intracranial hemorrhage, or bleeding that causes hemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention

Moderate: Bleeding that leads to transfusion but does not meet criteria for severe bleeding
5429 patients screened with VerifyNow P2Y12 12-24 hours post-PCI

2214 (41%) with high residual platelet reactivity (PRU ≥ 230)

3215 (59%) without high residual platelet reactivity (PRU < 230)

- Clopidogrel High Dose N=1109
- Clopidogrel Standard Dose N=1105
- Clopidogrel Standard Dose N=586

Non-Randomized Comparison

Random selection
Secondary Comparison: High vs. Not High Reactivity
Treated with Clopidogrel 75-mg daily

2.3% vs. 1.4%
HR 1.68 (95% CI 0.76, 3.72)
p=0.20

Observed event rates are listed. P value by log-rank test.
CV Events and Post-PCI PRU In Patients With High and Not High Reactivity Treated With Clopidogrel 75-mg Daily

PRU 12 - 24 hrs post-PCI

Red dots: patients with CV death, MI, or ST

High Residual Reactivity

Not High Residual Reactivity

ITT population
In patients with high residual reactivity measured after PCI, 6-months of high-dose clopidogrel did not reduce the rate of cardiovascular death, non-fatal MI, or stent thrombosis and did not increase GUSTO severe or moderate bleeding.
GRAVITAS does not support a treatment strategy of high-dose clopidogrel in patients with high residual reactivity identified by a single platelet function test after PCI.
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 PHRI, McMaster University and the trial was overseen by an international steering committee of experts.
Study Design

25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)

- Planned Early (<24 h) Invasive Management with intended PCI
- Ischemic ECG Δ (80.8%) or ↑ 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

Compliance:
Complete F/U 99.8%

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
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>
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<tbody>
<tr>
<td>CV Death/MI/Stroke</td>
<td></td>
<td></td>
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<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>
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<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>
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<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>
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<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>
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<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>
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<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>
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<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>
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</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: Double vs Standard Dose

## Primary Outcome and Components

<table>
<thead>
<tr>
<th>Event</th>
<th>Standard</th>
<th>Double</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
<th>Intn P</th>
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<tr>
<td><strong>CV Death/MI/Stroke</strong></td>
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<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>
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<td>No PCI (2N=7855)</td>
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<td>0.95-1.44</td>
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<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>
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<td><strong>MI</strong></td>
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<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>
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<td>No PCI (2N=7855)</td>
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<td>1.25</td>
<td>0.87-1.79</td>
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<td>Overall (2N=25,087)</td>
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<td>0.86</td>
<td>0.73-1.03</td>
<td>0.097</td>
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<td><strong>CV Death</strong></td>
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<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>
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<td>No PCI (2N=7855)</td>
<td>2.8</td>
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<td>0.74-1.26</td>
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<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>
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<td><strong>Stroke</strong></td>
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<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>
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<td>No PCI (2N=7855)</td>
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<tr>
<td>Overall (2N=25,087)</td>
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<td>0.99</td>
<td>0.70-1.39</td>
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### Clopidogrel Double vs Standard Dose Bleeding Overall Population

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<tr>
<th></th>
<th>Clopidogrel</th>
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<th>Hazard</th>
<th>95% CI</th>
<th>P</th>
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<td>Standard</td>
<td>Double</td>
<td>Ratio</td>
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<tr>
<td></td>
<td>N=12579</td>
<td>N=12508</td>
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<tr>
<td>TIMI Major(^1)</td>
<td>0.95</td>
<td>1.04</td>
<td>1.09</td>
<td>0.85-1.40</td>
<td>0.50</td>
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<tr>
<td>CURRENT Major(^2)</td>
<td>2.0</td>
<td>2.5</td>
<td>1.25</td>
<td>1.05-1.47</td>
<td>0.01</td>
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<tr>
<td>CURRENT Severe(^3)</td>
<td>1.5</td>
<td>1.9</td>
<td>1.23</td>
<td>1.02-1.49</td>
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<td>Fatal</td>
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<td>0.13</td>
<td>1.15</td>
<td>0.56-2.35</td>
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<td>0.03</td>
<td>0.67</td>
<td>0.19-2.37</td>
<td>0.53</td>
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<td>RBC transfusion ≥ 2U</td>
<td>1.76</td>
<td>2.21</td>
<td>1.26</td>
<td>1.06-1.51</td>
<td>0.01</td>
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<td>CABG-related Major</td>
<td>0.9</td>
<td>1.0</td>
<td>1.10</td>
<td>0.85-1.42</td>
<td>0.48</td>
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</table>

\(^1\)ICH, Hb drop ≥ 5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal

\(^2\)Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units

\(^3\)Fatal or ↓Hb ≥ 5 g/dL, sig hypotension + inotropes/surgery, ICH or txn of ≥ 4 units
Clopidogrel: Double vs Standard Dose
Definite Stent Thrombosis (Angio confirmed)

- Clopidogrel Standard Dose
- Clopidogrel Double Dose

Cumulative Hazard

Days

0 3 6 9 12 15 18 21 24 27 30

HR 0.58
95% CI 0.42-0.79
P=0.001

42% RRR
Clopidogrel: Double vs Standard Dose
Major Efficacy Outcomes in PCI Patients

<table>
<thead>
<tr>
<th>Day 30</th>
<th>Clopidogrel</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P value</th>
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<tbody>
<tr>
<td></td>
<td>Standard N=8684 %</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Double N=8548 %</td>
<td></td>
<td></td>
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<tr>
<td>Stent Thrombosis</td>
<td>2.3</td>
<td>1.6</td>
<td>0.71</td>
<td>0.57-0.89</td>
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<tr>
<td>Stent Thrombosis, Definite</td>
<td>1.2</td>
<td>0.7</td>
<td>0.58</td>
<td>0.42-0.79</td>
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<td>MI</td>
<td>2.6</td>
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<td>0.78</td>
<td>0.64-0.95</td>
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<td>MI or stent thrombosis</td>
<td>3.7</td>
<td>3.0</td>
<td>0.80</td>
<td>0.68-0.94</td>
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<tr>
<td>CV Death</td>
<td>1.9</td>
<td>1.9</td>
<td>0.96</td>
<td>0.77-1.19</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.4</td>
<td>0.4</td>
<td>0.88</td>
<td>0.55-1.41</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>
</tr>
</tbody>
</table>
Clopidogrel: Double vs Standard Dose Primary Outcome in PCI Patients

CV Death, MI or Stroke

Clopidogrel Standard

Clopidogrel Double

15% RRR

HR 0.85
95% CI 0.74-0.99
P=0.036
## Clopidogrel Double vs Standard Dose Bleeding in PCI Population

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel Standard N= 8684</th>
<th>Clopidogrel Double N=8548</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI Major^1</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 Major^2</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 Severe^3</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
Conclusions
Clopidogrel Dose Comparison

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

- 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).

- 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.
Due to difference in design, patient populations, length of treatment and follow-up of these clinical studies, it is not appropriate to make cross-trial comparisons but these clinical studies enable cardiologists to have more scientific discussion about the issue of optimal Clopidogrel regimen.
Thank you for your attention!