Randomized Trial of 75 mg vs 150 mg of Daily Clopidogrel in Patients Undergoing PCI

Adnan Kastrati

Deutsches Herzzentrum, Munich, GERMANY
Variability in Platelet Response to Clopidogrel

Serebruany et al, JACC 2005
Variability Sources

Potential Sites for Response Variability

- Intestinal Absorption
- Hepatic Metabolism
  - Cytochrome P450 pathway
- Active Metabolite
- P2Y_{12} Receptor (irreversible inhibition)
- GP IIb/IIIa receptor expression

- Poor compliance
- Inadequate administration
- Variable absorption
- Drug-drug interactions
- Genetic polymorphisms CYP enzymes
- Drug-drug interactions
- Genetic polymorphisms P2Y_{12} receptor
- Alternate pathways of platelet activation
  - Release of circulating ADP
  - Higher baseline platelet reactivity
- Genetic polymorphisms

Figure 4. Proposed mechanisms for interindividual variability in platelet inhibition in response to clopidogrel. GP indicates glycoprotein.

O’Donoghue & Wiviott, Circ 2006
How can we measure platelet response to clopidogrel in clinical practice?
Light Transmission Aggregometry

Platelet Aggregation Profiler® PAP 8
(Bio/Data Corporation, USA)

Standard method, but complex, time-consuming and impractical for routine use
Whole-Blood Aggregometry

Multiple Platelet Function Analyzer®
(Dynabyte GmbH)

Post-600mg Clopidogrel ADP test (AUC)

R=0.76

No. of pts
Point of Care Assay

VerifyNow® P2Y12 Assay
(Accumetrics, USA)

No. of pts

Post-600mg Clopidogrel Reactivity (PRUs)

$R = 0.86$
Case illustrations
Patient with Stent Thrombosis
72h After Procedure
Results of LT Aggregometry
20h After 600 mg of Clopidogrel

ADP 5μM

ADP 20μM
Results of Whole Blood Aggregometry 20h After 600 mg of Clopidogrel

ST patient

AUC=1196*AU*min

Control

AUC=297*AU*min
A Patient with Stent Thrombosis and Clopidogrel Resistance

Beckerath et al, Thromb Haemost 2005
A Patient with Stent Thrombosis and Failed Clopidogrel Metabolism

**A**

![Graph A](image1)  
Time (hours)  
Clopidogrel (ng/ml)  
- ST patient  
- Control

**B**

![Graph B](image2)  
Time (hours)  
Active Metabolite (ng/ml)  
- ST patient  
- Control

Beckerath et al, Thromb Haemost 2005
EXCELSIOR Study
802 pts

600mg of clopidogrel
Light transmission aggregometry (5µM ADP) prior to PCI
Platelet Aggregation During PCI and Outcome

30-day MACE (%)

![Graph showing 1st, 2nd, 3rd, and 4th quartiles with corresponding statistics.]

- 1st quartile: (< 4%) - 1/209
- 2nd quartile: (4 – 13%) - 1/198
- 3rd quartile: (14 – 32%) - 6/196
- 4th quartile: (> 32%) - 7/199

p = 0.034

ADP-induced (5 µM) platelet aggregation

EXCELSIOR, JACC 2006
Clinical Relevance of Nonresponse to Clopidogrel

RECLOSE Trial
804 DES pts

600mg of clopidogrel
Light transmission aggregometry (ADP 10µmol)
Non-respondent pts – upper 10% of aggregation

LBCT of Dr. Antoniucci at ACC ‘07
## RECLOSE Trial

### Primary End Point

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Resp.</th>
<th>Non- Resp.</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td><strong>Six-month FU</strong></td>
<td>n=804</td>
<td>n=699</td>
<td>n=105</td>
<td></td>
</tr>
<tr>
<td>Definite/probable stent thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>25 (3.1)</td>
<td>16 (2.3)</td>
<td>9 (8.6)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Probable</td>
<td>14 (1.7)</td>
<td>7 (1.0)</td>
<td>7 (6.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Time of stent thrombosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Subacute</td>
<td>16 (2.0)</td>
<td>12 (1.7)</td>
<td>4 (3.8)</td>
<td>0.152</td>
</tr>
<tr>
<td>Late</td>
<td>9 (1.1)</td>
<td>4 (0.6)</td>
<td>5 (4.8)</td>
<td>&lt; 0.001</td>
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</tbody>
</table>
Evidence on Increased Loading Dose
Platelet Inhibition After 300, 600 and 900 mg of Clopidogrel

n=45, point of care test (Accumetrics)

Price et al, AJC 2006
Platelet Inhibition After 300, 600 and 900 mg of Clopidogrel

n=103, optical aggregometry

ALBION trial, JACC 2006
Platelet Inhibition After 300, 600 and 900 mg of Clopidogrel

n=60, optical aggregometry

ADP(5 μmol/L)-Induced Aggregation (%) vs. Dosage

- 300 mg: P=0.01
- 600 mg: P=0.001
- 900 mg: P=0.59

ISAR-CHOICE, Circulation 2005
Plasma Concentrations

Active metabolite

Clopidogrel

ISAR-CHOICE, Circulation 2005
Evidence on Increased Maintenance Dose
Are Clopidogrel Maintenance Doses >75 mg More Effective?

600 mg Loading in Pts on 75 mg Chronic Therapy

P<0.001

ADP (5µmol/L)-Induced Aggregation, %

Before loading

After loading

600 mg Clopidogrel

Kastrati et al, Circulation 2004
ISAR-CHOICE 2
- A Double Blind Study-

60 Patients

150 mg 75 mg

No. of patients 31 29
Daily 150 or 75 mg clopidogrel

600 mg clopidogrel

0

30 days

assessment of platelet function
(optical aggregometry, 5 & 20 µmol/L ADP
Point of care test: Verify Now)
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>150 mg n=31</th>
<th>75 mg n=29</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>63.0±7.5</td>
<td>65.4±6.9</td>
<td>0.20</td>
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<tr>
<td><strong>Women</strong></td>
<td>3 (9.7)</td>
<td>2 (6.9)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>89.2±17.4</td>
<td>82.8±9.8</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>176.2±6.8</td>
<td>174.8±6.5</td>
<td>0.41</td>
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<tr>
<td><strong>Platelet count, 10⁹/L</strong></td>
<td>217±65</td>
<td>223±44</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Arterial hypertension</strong></td>
<td>14 (45.2)</td>
<td>15 (51.7)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>16 (51.6)</td>
<td>142 (48.3)</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>Active smoker</strong></td>
<td>3 (9.7)</td>
<td>2 (6.9)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>7 (22.6)</td>
<td>10 (34.5)</td>
<td>0.31</td>
</tr>
</tbody>
</table>
### Baseline Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>150 mg n=31</th>
<th>75 mg n=29</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>31 (100)</td>
<td>29 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>28 (90.3)</td>
<td>28 (96.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>27 (87.1)</td>
<td>26 (89.7)</td>
<td>0.76</td>
</tr>
<tr>
<td>Statins</td>
<td>31 (100)</td>
<td>28 (96.6)</td>
<td>0.48</td>
</tr>
</tbody>
</table>
Aggregometry (30 days)

ADP(5 µmol/L)-Induced Aggregation (%)

150 mg/day

75 mg/day

Clopidogrel

P<0.001
Aggregometry (30 days)

ADP(20 µmol/L)-Induced Aggregation (%)

- 150 mg/day
- 75 mg/day

Clopidogrel

$P < 0.001$

$P < 0.001$
VerifyNow™ P2Y12 Assay (30 days)

P2Y12 Reaction Units

<table>
<thead>
<tr>
<th>Clopidogrel</th>
<th>150 mg/day</th>
<th>75 mg/day</th>
</tr>
</thead>
</table>

P = 0.004
VerifyNow™ P2Y12 Assay (30 days)

$P=0.006$

% Inhibition

150 mg/day 75 mg/day

Clopidogrel
Conclusions, I

- A low platelet response to clopidogrel is observed in a relevant proportion of patients.
- Increase in the loading dose of clopidogrel up to 600 mg is able to improve significantly platelet response to clopidogrel.
Doubling maintenance dose to 150 mg leads to stronger platelet inhibition.

This maintenance dose may turn out to be useful in high risk patients or patients with limited response to clopidogrel.

The clinical efficacy and safety of this increased dose regimen need to be evaluated in specifically designed RCTs.