Is the 3rd agent a solution for the resistance against anti-platelet agents?

CILostazol On Neointimal growth and Thrombotic events in drug-eluting stents (CILON-T) trial

Jung-Won Suh , Hyo-Soo Kim MD, PhD

Seoul National University College of Medicine

SNUH Cardiovascular Center

Bundang SNUH Cardiovascular Center
Clopidogrel: mechanism

**A**
- ADP → P2Y₁₂ coupled → cAMP
- Platelet → Fibrinogen receptor activation → Thromboxane A₂ generation → Sustained aggregation response

**B**
- CYP450 3A
- Clopidogrel → Oxidation → Active metabolite
- Platelet → No fibrinogen receptor activation → No thromboxane A₂ generation → No aggregation response
Causes of Clopidogrel Resistance

- Absorption

- P2Y12 Rc polymorphism
  - Controversial
  - Pro; Cerebrovascular ds (Ziegler S, Stroke 2005), PAD (Fontana P, Circulation 2003)
  - Cons; CAD (Smith SM, Platelets 2006/ Angiolillo DJ, Thromb Res 2005)

- Metabolism, Drug interaction
  - CYP3A5 polymorphism (Suh JW, et al. CMAJ 2006)
Implication of Clopidogrel Resistance

Clopidogrel Resistance Is Associated With Increased Risk of Recurrent Atherothrombotic Events in Patients With Acute Myocardial Infarction

Shlomi Matetzky, MD; Boris Shenkman, MD, PhD; Victor Guetta, MD; Michael Shechter, MD; Roy Bienart, MD; Ilan Goldenberg, MD; Ilya Novikov, PhD; Hanna Pres, MSc; Naphtali Savion, PhD; David Varon, MD; Hanoch Hod, MD
# Implication of Clopidogrel Resistance

## Clopidogrel Effect on Platelet REactivity in Patients With Stent Thrombosis

Results of the CREST Study

Paul A. Gurbel, MD, FACC, Kevin P. Bliden, BS, Waiel Samara, MD Jason A. Yoho, MD, Kevin Hayes, MD, Mulugeta Z. Fissha, MD, Udaya S. Tantry, PhD

*Baltimore, Maryland*

<table>
<thead>
<tr>
<th></th>
<th>SAT (n = 20)</th>
<th>No SAT (n = 100)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTA (5 μmol/l ADP) (%)</td>
<td>49 ± 4</td>
<td>33 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LTA (20 μmol/l ADP) (%)</td>
<td>65 ± 3</td>
<td>51 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LTA (1 mmol/l arachidonic acid)</td>
<td>1 non-responder</td>
<td>0 non-responders</td>
<td></td>
</tr>
<tr>
<td>P2Y$_{12}$ reactivity ratio (%)</td>
<td>69 ± 5</td>
<td>46 ± 9</td>
<td>0.03</td>
</tr>
<tr>
<td>GP IIb/IIIa (MFI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstimulated</td>
<td>9 ± 1</td>
<td>15 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Stimulated</td>
<td>138 ± 19</td>
<td>42 ± 4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
What can we do for ‘resistant’ patients?
Dose up

- Aspirin; controversial
  - BRAVO-2, CURE; Major bleeding risk ↑

- Clopidogrel
  - Increase of loading dose: 600mg > 300mg
    - ARMYDA-2, ALBION, ISAR-CHOICE
  - Double maintenance dose in high risk patients: 150mg > 75mg
    - Type 2 DM in OPTIMUS
Compliance

- Schwartz KA et al. (AJC 2005)
  - Usual dose of daily aspirin (9%)
  - 2hrs after direct observed therapy of aspirin 325mg (<1%)

- Premature discontinuation of clopidogrel
  - Most important risk factor of stent thrombosis
  - HR 89.78 (C.I 29.9-269.60, p<0.001, JAMA 2006)
Control of Comorbidities

- Hyperglycemia
- HyperTG
- Active inflammation
- Congestive heart failure
- Catecholamine surge
Drug interaction

- **Aspirin**
  - Omeprazole
  - NSAIDs; Ibuprofen, Indomethacin

- **Clopidogrel; via CYP3A**

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Diltiazem, Verapamil, Nifedipine, Losartan, Atorvastatin, metoprolol, Benzodiazepine, Cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inducers</td>
<td>Rifampin, Alcohol, Phenobarbital, Phenytoin sodium, Carbamazepine</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>Ketoconazole, Itraconazole, Grapefruit juice, Clarithromycin, Erythromycin, Cimetidine, Nefazodone, Protease inhibitors, Verapamil</td>
</tr>
</tbody>
</table>
CYP3A5 SNP & Clopidogrel Drug Interaction

(Suh JW, et al. CMAJ 2006)

**Lipophilic statin, metoprolol, diltiazem, nifedipine, losartan, cimetidine**

**A** Clopidogrel alone

- **CYP3A5 expressor genotype (**1/1/**1/3)**
  - 3A4 activity
  - 3A5 activity

- **CYP3A5 non-expressor genotype (**3/3)**
  - 3A4 activity
  - 3A5 activity

No platelet aggregation

**B** Clopidogrel in the presence of substrates or inhibitors

- **CYP3A5 expressor genotype (**1/1/**1/3)**
  - 3A4 activity
  - 3A5 activity

- **CYP3A5 non-expressor genotype (**3/3)**
  - 3A4 activity

Platelet aggregation

---

**Graphs**

- **Non-expressor genotype**
  - p < 0.001
  - Baseline 4 h 24 h 6 d

- **Expressor genotype**
  - p < 0.001
  - Baseline 4 h 24 h 6 d

**Graphs**

- **Non-expressor genotype**
  - NS
  - Baseline 4 h 24 h 6 d

- **Expressor genotype**
  - p < 0.001
  - Baseline 4 h 24 h 6 d
# CYP3A5 SNP & Clopidogrel Drug Interaction

(Suh JW, et al. CMAJ 2006)

## Table 3: Clinical outcomes after coronary angioplasty and bare-metal stent implantation, by CYP3A5 genotype

<table>
<thead>
<tr>
<th>Outcome after stent implantation</th>
<th>CYP3A5 genotype; no. of patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-expressor n = 193, Expressor n = 155</td>
<td></td>
</tr>
<tr>
<td>At 1 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI (subacute thrombosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonhemorrhagic stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-6 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden death</td>
<td>0, 0</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>4, 0</td>
<td></td>
</tr>
<tr>
<td>Nonhemorrhagic stroke</td>
<td>0, 0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4, 0</td>
<td>0.10</td>
</tr>
<tr>
<td>6-mo cumulative</td>
<td>14, 3</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Note: MI = myocardial infarction.

## Table 4: Risk factors for atherothrombotic events after coronary angioplasty and bare-metal stent implantation among patients taking clopidogrel

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A5 non-expression (v. expression)</td>
<td>3.96 (1.12-14.0)</td>
<td>4.89 (1.28-18.7)</td>
</tr>
<tr>
<td>Co-administered CYP3A metabolisers† (every increase in no.)</td>
<td>2.15 (1.15-4.03)</td>
<td>2.22 (1.10-4.47)</td>
</tr>
<tr>
<td>Age ≥ 65 yr (v. &lt; 65 yr)</td>
<td>0.98 (0.94-1.03)</td>
<td>0.98 (0.93-1.03)</td>
</tr>
<tr>
<td>Male sex (v. female)</td>
<td>1.74 (0.64-4.70)</td>
<td>2.08 (0.65-6.61)</td>
</tr>
<tr>
<td>Previous MI (v. no previous MI)</td>
<td>0.80 (0.22-2.86)</td>
<td>0.72 (0.17-3.10)</td>
</tr>
<tr>
<td>Diabetes mellitus (v. no diabetes)</td>
<td>1.52 (0.57-4.05)</td>
<td>1.15 (0.39-3.40)</td>
</tr>
<tr>
<td>LV systolic ejection fraction &lt; 45% (v. &gt; 45%)</td>
<td>1.12 (0.25-5.07)</td>
<td>1.13 (0.20-6.34)</td>
</tr>
<tr>
<td>Stent diameter ≥ 2.75 mm (v. &lt; 2.75 mm)</td>
<td>0.89 (0.36-2.23)</td>
<td>0.66 (0.24-1.85)</td>
</tr>
<tr>
<td>Stent length ≥ 20 mm (v. &lt; 20 mm)</td>
<td>0.99 (0.92-1.06)</td>
<td>0.98 (0.91-1.06)</td>
</tr>
</tbody>
</table>
# Clopidogrel Alternatives: P2Y12 Receptor Antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Structure</th>
<th>Direct or Indirect</th>
<th>Reversible</th>
<th>Route</th>
<th>Frequency</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticlopidine</td>
<td>Thienopyridine</td>
<td>I</td>
<td>No</td>
<td>PO</td>
<td>Twice/day</td>
<td>Approved</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Thienopyridine</td>
<td>I</td>
<td>No</td>
<td>PO</td>
<td>Daily</td>
<td>Approved</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Thienopyridine</td>
<td>I</td>
<td>No</td>
<td>PO</td>
<td>Daily</td>
<td>3</td>
</tr>
<tr>
<td>AZD6140</td>
<td>ATP analog</td>
<td>D</td>
<td>Yes</td>
<td>PO</td>
<td>Twice/day</td>
<td>3</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>ATP analog</td>
<td>D</td>
<td>Yes</td>
<td>IV</td>
<td>…</td>
<td>3</td>
</tr>
<tr>
<td>PRT60128</td>
<td>…</td>
<td>D</td>
<td>Yes</td>
<td>PO, IV</td>
<td>…</td>
<td>1</td>
</tr>
</tbody>
</table>

*Michelson AD, Arterioscler Thromb Vasc Biol 2008*
Clopidogrel Alternatives: Structures

THIENOPYRIDINES

- Ticlopidine
- Clopidogrel
- Prasugrel

ACTIVE METABOLITES

- HOOC-\(\text{Cl}\)
- HOOC-\(\text{N}\)-\(\text{Cl}\)
- HOOC-\(\text{N}\)-\(\text{F}\)

A TP analogs

- ATP
- AR-C109318XX
- AR-C69931MX (Cangrelor)
- AZD6140

Michelson AD. Arterioscler Thromb Vasc Biol 2008
Clopidogrel Alternative; under investigation

- **Prasugrel**
  - Oral thienopyridine
  - TRITON-TIMI 38
  - More rapid & potent, but high bleeding risk

- **Cangrelor**
  - IV form, direct antagonist of P2Y12 Rc
  - No liver metabolism, potent, short action, facilitated PCI
  - CHAMPION-PCI, CHAMPION-PLATFORM: ongoing

- **AZD6140**
  - Oral ADP antagonist
  - Potency, no liver metabolism
  - PLATO: ongoing
Another antiplatelet agent on top of dual agents

- Triflusal
  - COX-1 / COX-2 inhibition
  - NO production

Suh JW, et al. unpublished
Cilostazol; anti-platelet effect

ADP $\rightarrow$ P2Y$_{12}$ coupled $\rightarrow$ Gi$_2$ $\rightarrow$ Cilostazol $\rightarrow$ PDE type3 $\rightarrow$ cAMP $\rightarrow$ Fibrinogen receptor activation $\rightarrow$ Thromboxane A$_2$ generation $\rightarrow$ Sustained aggregation response
Cilostazol; Other actions → restenosis or CIN?

- Vasodilation via VSMC
  - Cerebral
  - Low extremities

- Scavenging ROS

- Prevention of cell apoptosis
  - Endothelial cell
  - Brain white matter
  - Renal tubular cell
The role of cAMP in RTC

Contrast dye

Porcine renal tubular cell

APOPTOSIS ↑
Caspase -3, 9, bax ↑, Bcl-2 ↓

Cilostazol?

Itoh Y et al, Kidney Int 2006
PK of cilostazol

**Excretion route (%)**
- Urine (74%)
- Feces (20%)
- Others (6%)

**Excretion forms (%)**
- Cilostazol (< 2%)
- 4’-trans-hydroxy-cilostazol (30%)
- 3,4-hydroxy cilostazol (5%)
- Others (63%)
  - None exceeds 5%
# CIN; mechanism

- **Ischemia d/t vasoconstriction**: Dopamine, Fenoldopam

- **Apoptosis by direct toxicity**: Theophylline

- **Apoptosis by oxidative stress**: NAC, Vit C

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*Cilostazol; Potential candidate of CIN prophylaxis?*
CILON-T trial

- CILostazol On Neointimal growth and Thrombotic events in drug-eluting stents
- *Seoul National University Hospital (SNUH)
  *Bundang SNUH
  *Konyang University Hospital
  *Korea University Guro Hospital
  *Gwangju Veterans Hospital
  *Chungbuk National University Hospital
Issues to be answered: background for CILON-T trial

- Statin type & drug interaction with clopidogrel
  - The role of CYP3A system in clopidogrel resistance
  - Head to head comparison of atorvastatin vs. rosvastatin

- Clopidogrel resistance and genetics

- Cilostazol use in DES era; thrombotic aspect

- Angiographic outcome according to stent type; late loss

- Nephro-protective effect of cilostazol
Protocol of CILONT

Day-1
Randomization (n=1000)

Cilostazol group (n=500)  Control group (n=500)

Day 0
PCI with DES & nonionic contrast dye

Day 1
CK, CK-MB, Troponin I at 24hr

1 month
Clinical outcome, complication

6 months
Clinical outcome, angiographic outcome, complication
Medication

- Cilostazol
  - D-1 or D0; 200mg qd
  - D1~D180; 100mg bid

- Antiplatelet agent; ASA (100mg) + Clopidogrel (75mg)

- CYP3A4 inhibitor / substrate
  - Avoid diltiazem, felodipine, nifedipine, cimetidine, erythromycin if possible

- Hydration
  - 0.9% saline for 48hrs
  - Avoid the use of NAC, ascorbic acid
Stratification by statin

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (20mg/day)</th>
<th>Rosuvastatin (10mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA+PLAVIX</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>ASA+PLAVIX+CILO</td>
<td>250</td>
<td>250</td>
</tr>
</tbody>
</table>
Endpoints

- **Primary Endpoint**
  - MACE within 6 months (cardiac death, MI, stroke, TLR)

- **Secondary Endpoint**
  - Scr, Random urine ACR: baseline /6mo
  - Angiographic outcome (late loss, binary restenosis)
  - Bleeding Cx (cerebral, intraocular, Tf ≥2units)
  - Platelet function test
    - VerifyNow P2Y12
    - Platelet volume indices (MPV, PDW)
    - Platelet aggregometry
  - Genetic analysis
Current Status (Mar 2008)

- Total enrollment (n=441, dual 233, triple 208)

- 6 Mo Interim analysis
  - Clinical F/U (n=278)
  - Noncardiac death 1 (suicide)
  - Cardiac death 1
  - MI d/t stent thrombosis 1
  - TLR (n=19), TVR (n=11)
## MACE (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Dual (n=138)</th>
<th>Triple (n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TLR</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Composites</td>
<td>14</td>
<td>7</td>
</tr>
</tbody>
</table>

P=0.12

*A case of pulmonary embolism in the dual group*
Platelet inhibition by cilostazol (6Mo F/U)

**PRU**

- Control: 257.4
- Cilostazol: 214.1
  
  $p < 0.001$

**% of P2Y12 Inhibition**

- Control: 17.7
- Cilostazol: 31.1

$\text{Control (n=109), Cilostazol (n=112)}$
Breakthrough of Clopidogrel Resistance?

<table>
<thead>
<tr>
<th>Resistance (+)</th>
<th>Dual (n=109)</th>
<th>Triple (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>34 (31.2%)</td>
<td>22 (19.6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resistance (-)</th>
<th>Dual (n=109)</th>
<th>Triple (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75 (68.8%)</td>
<td>90 (80.4%)</td>
</tr>
</tbody>
</table>

*p = 0.06

** Resistance: Highest Quartile of PRU (>286 unit)
**Breakthrough of Clopidogrel Resistance?**

<table>
<thead>
<tr>
<th></th>
<th>Dual (n=109)</th>
<th>Triple (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance (+)</td>
<td>50 (45.9%)</td>
<td>29 (25.9%)</td>
</tr>
<tr>
<td>Resistance (-)</td>
<td>59 (54.1%)</td>
<td>83 (74.1%)</td>
</tr>
</tbody>
</table>

*p = 0.002

**Resistance**: P2Y12 inhibition <10%
## Platelet inhibition by cilostazol & statin type

<table>
<thead>
<tr>
<th>6 Mo</th>
<th>Atorva / Con (n=50)</th>
<th>Atorva / Cilo (n=51)</th>
<th>Rosuva / Con (n=50)</th>
<th>Rosuva / Cilo (n=46)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2Y12 inhibition (%)</td>
<td>16.8±18.4</td>
<td>32.4±23.4</td>
<td>18.6±19.9</td>
<td>35.3±24.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Absolute PRU (unit)</td>
<td>256.7±59.2</td>
<td>206.9±74.9</td>
<td>246.4±73.9</td>
<td>203.2±81.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
P2Y12 inhibition at 6 Mo

Atorva/Con  | Atorva/Cilo  | Rosuva/Con  | Rosuva/Cilo

*** <0.001  ** <0.01  * <0.05
Absolute PRU level at 6 Mo

Atorva/Con    Atorva/Cilo    Rosuva/Con    Rosuva/Cilo

*** <0.001 ** <0.01 * <0.05
Pts with clopidogrel resistance: Interaction with statin?

- Pts with highest quartile PRU (PRU > 283)

![Bar chart showing percentages]

- Atorva/Con: 36.0%
- Atorva/Cilo: 17.6%
- Rosuva/Con: 28.0%
- Rosuva/Cilo: 17.4%
Summary

- Clopidogrel resistance is clinically important.
- The interaction of statin type with clopidogrel resistance is not conclusive yet, but should be examined with follow up data of CILON-T trial.
- Cilostazol can be a good candidate of breakthrough of clopidogrel resistance.
- Drug interaction & CYP 3A5 genotype; pending
- Nephro-protective effect of cilostazol; pending
Is the 3rd agent a solution for the resistance against dual anti-platelet agents?

Yes, it can be.