The Role of Triple Antiplatelet Therapy in Patients with High Risk

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**Metabolic Pathways blocked By Statins**

Statins block the pathway from Acetyl-CoA + Acetoacetyl-CoA to HMG-CoA, ultimately leading to Squalene and Cholesterol. Statins affect the early/rapid and later benefit related to hepatic LDL reduction. They also influence prenylation, which is important in vascular cellular responses.

- **Early/Rapid and Later Benefit** (pleiotropic effect)
  - Important in vascular cellular responses
  - Translocates to the cell membrane

**Acetyl-CoA + Acetoacetyl-CoA**

↑

**Statins**

↓

**HMG-CoA**

**Mevalonate**

↓

**Isopentanyl PP**

↓

**Geranyl PP**

↓

**Farnesyl PP** → **Geranyl Geranyl PP** → **Rho**

**Squalene**

↓

**Cholesterol**

**PP = pyrophosphate.**
Pleiotropic Effects of Statin

- Effects on VSMC growth
- Endothelial function (NO regulation)
- Atherosclerotic plaque stabilization
- Inhibition of LDL-C oxidation
- Reduced leukocyte adhesiveness
- Reduced ischemia-reperfusion injury (cardiac and cerebral)
- Enhanced angiogenesis
- Platelet inhibition and anti-thrombosis

Pleiotropic Effects of Cilostazol


- Inhibition of VSMC growth
  Stimulation of p53 and p21 (Matsushita H. Hypertension 1998;31:493.)

- Restoration of Endothelial dysfunction
  Up-regulation of HGF (Aoki M. Diabetologia 2001;44:1034.)

- Atherosclerotic plaque stabilization

- Reduced leukocyte adhesiveness
  Inhibition of CAM expression (Otsuki M. Atherosclerosis 2001;158:121.)

- Reduced ischemia-reperfusion injury (cardiac and cerebral)
  Activation of PTEN (Kim KY, et al. JPET 2004;308:97.)

- Enhanced angiogenesis

- Platelet inhibition and anti-thrombosis
The Role of Cilostazol

<table>
<thead>
<tr>
<th>Targets</th>
<th>cAMP actions (selected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cilostazol</td>
<td></td>
</tr>
<tr>
<td>PDE3A</td>
<td>• Inhibition of aggregation</td>
</tr>
<tr>
<td>Adenosine</td>
<td>• Inhibition of expression of adhesion molecules</td>
</tr>
<tr>
<td>ATP</td>
<td></td>
</tr>
<tr>
<td>cAMP↑</td>
<td>• Inhibition of expression of adhesion molecules</td>
</tr>
<tr>
<td>5’AMP</td>
<td>• Angiogenesis</td>
</tr>
<tr>
<td>platelet</td>
<td></td>
</tr>
<tr>
<td>endothelial cell</td>
<td>• Vasodilatory action</td>
</tr>
<tr>
<td>smooth muscle cell</td>
<td>• Inhibition of proliferation, migration and matrix synthesis</td>
</tr>
<tr>
<td>cardiocyte</td>
<td>• Headache</td>
</tr>
<tr>
<td>A2</td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td></td>
</tr>
</tbody>
</table>

Summit TCT Asia Pacific 2009
Role of cAMP / Protein Kinase A

- cAMP
- g
- a
- AC
- ATP
- ADP
- Nucleus
- PKA catalytic subunit
- phosphorylates CREB
- and activates transcription

Inactive protein kinase A (PKA)
- Regulatory subunit of PKA binds cAMP
- dissociates from the catalytic subunit
- Free PKA catalytic subunit migrates to nucleus

Altered Protein Function

Altered Gene Expression

- PKA can phosphorylate many different proteins depending on tissue type and status
- PKA can activate enzymes or gene regulatory proteins
Pleiotropic Effects of Cilostazol


- **Inhibition of VSMC growth**
  Stimulation of p53 and p21 (Matsushita H. Hypertension 1998;31:493.)

- **Restoration of Endothelial dysfunction**
  Up-regulation of HGF (Aoki M. Diabetologia 2001;44:1034.)

- **Atherosclerotic plaque stabilization**

- **Reduced leukocyte adhesiveness**
  Inhibition of CAM expression  (Otsuki M. Atherosclerosis 2001;158:121.)

- **Reduced ischemia-reperfusion injury** (cardiac and cerebral)
  Activation of PTEN (Kim KY, et al. JPET 2004;308:97.)

- **Enhanced angiogenesis**

- **Platelet inhibition and anti-thrombosis**
Aspirin Resistance is rare. Low dose aspirin (- 162mg/d) achieves adequate inhibition of COX-1 pathway.


Clopidogrel variably inhibits ADP-induced platelet aggregation. Adequate platelet inhibition by potent P2Y12 antagonists may suppress the risk of ischemic events in pts with high risk.

Cilostazol achieves about 70 – 80% inhibition of ADP-induced platelet aggregation compared to Clopidogrel.
Cilostazol vs Clopidogrel Therapy After BMS Implantation


* AMI were due to stent thrombosis
Triple versus Dual Antiplatelet Therapy

TAPT reduces the risk of ST by 88% compared to DAPT.
It may be related with additive inhibition of ADP-induced platelet aggregation by Adjunct Cilostazol.

Predictors of stent thrombosis
1. Primary stenting for AMI
   (OR 7.9, 95% CI 2.0-30.8, p = 0.003)
2. TAPT (OR 0.12, 95% CI 0.015-0.98, p = 0.048)

### Safety of triple antiplatelet therapy

<table>
<thead>
<tr>
<th>Safety Outcomes</th>
<th>DAPT (n=1597)</th>
<th>TAPT (n=1415)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major bleeding</strong></td>
<td>10 (0.6%)</td>
<td>11 (0.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Vascular complication</td>
<td>9 (0.5%)</td>
<td>4 (0.3%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Adverse side effect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3 (0.2%)</td>
<td>2 (0.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (0.2%)</td>
<td>2 (0.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Elevated LFT</td>
<td>2 (0.1%)</td>
<td>1 (0.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>GI trouble</td>
<td>8 (0.5%)</td>
<td>3 (0.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Skin rash</td>
<td>8 (0.5%)</td>
<td>15 (1.1%)</td>
<td>0.079</td>
</tr>
</tbody>
</table>

Postulated Modulation of P2Y12 Receptor Signalling

Platelet aggregation
Triple vs. Dual therapy

Results are expressed as the mean value ± SD.
† p<0.05, ‡ p<0.01 between two groups.


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OPTIMUS-2: Impact of adjunctive cilostazol in Diabetes Mellitus patients on aspirin and clopidogrel

Primary Endpoint
P2Y\textsubscript{12} reactivity index (PRI)

\[ p<0.0001 \]

High MD Clopidogrel of 150mg/d in DM Pts

OPTIMUS-1 study

40 suboptimal responders (20μmol/L ADP-induced Agg\textsubscript{max} > 50%) with DM

- A 150-mg MD of clopidogrel is associated with enhanced antiplatelet effects compared with 75-mg in high risk T2DM pts.

- **Suboptimal clopidogrel response** is still present in 60% pts of 150mg regimen.

ADP-induced platelet inhibition in patients with high risk?

High MD CLPD vs. TAPT
HPPR: High Post-treatment Platelet Reactivity

1. ADP-induced platelet inhibition in patients with HPPR?

High MD CLPD vs. TAPT
**Adjunctive Cilostazol vs. high-MD Clopidogrel in HPPR (ACCEL study)**

*High Post-CLPD Platelet Reactivity (HPPR): maximal aggregation > 50% with 5 μM ADP*

Total patients that assess baseline platelet function (n=300)
- CLPD 300mg LD at least 12 h before procedure

- Met exclusion criteria (n=235)
  - Optimal response to clopidogrel, acute myocardial infarction, etc

Patients undergoing stenting with HPPR*

Randomization

- Triple therapy (n=30)
- High MD clopidogrel (n=30)

Platelet function test after 30-day therapy

Inhibition of maximal platelet aggregation (%)

IPA of Agg$_{max}$


- **5 μmol/L ADP**
  - High MD group: 28.0 ± 19
  - Triple group: 51.1 ± 23
  - **p < 0.001**

- **20 μmol/L ADP**
  - High MD group: 20.7 ± 16
  - Triple group: 39.6 ± 23
  - **p < 0.001**
Rate of HPPR (5 μmol/L ADP-induced Agg_{max} > 50%)


Rate of HPPR after 30-days therapy:
- **High MD group**: 26.7%
- **Triple group**: 3.3%

\[ p = 0.012 \]
Randomized Comparison of Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With High Post-Treatment Platelet Reactivity

Results of the ACCEL-RESISTANCE (Adjunctive Cilostazol versus High Maintenance Dose Clopidogrel in Patients With Clopidogrel Resistance) Randomized Study

Young-Hoan Jeong, MD, PhLD,* Seung-Whan Lee, MD, PhLD,† Bong-Ryong Choi, MD,* In-Suk Kim, MD, PhLD,† Myung-Ki Seo, MD,* Choong Hwan Kwak, MD, PhLD,* Jin-Yong Hwang, MD, PhLD,* Seong-Wook Park, MD, PhLD†

Jinju and Seoul, Korea

Objectives

The purpose of this study was to determine the impact of adjunctive cilostazol in patients with high post-treatment platelet reactivity (HPPR) undergoing coronary stenting.

Conclusion

Adjunctive cilostazol reduces the rate of HPPR and intensifies platelet inhibition as compared with a high-MD clopidogrel of 150 mg/day. (J Am Coll Cardiol 2009;53:1101–9) © 2009 by the American College of Cardiology Foundation
2. ADP-induced platelet inhibition in patients with AMI?

High MD CLPD vs. TAPT
TAPT vs. DAPT in pts with ACS

ACS pts undergoing successful coronary stenting (n=1212)

Randomization

TAPT (n=604):
Cilostazol 100mg bid for 6 mo.

DAPT (n=608)

1-yr Follow-up MACCE: cardiac death, MI, stroke, TVR

## One-year Clinical Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>DAPT (n=608)</th>
<th>TAPT (n=604)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>20 (3.3%)</td>
<td>10 (1.7%)</td>
<td>0.067</td>
</tr>
<tr>
<td>MI</td>
<td>4 (0.7%)</td>
<td>2 (0.3%)</td>
<td>0.687</td>
</tr>
<tr>
<td>Stroke</td>
<td>10 (1.6%)</td>
<td>4 (0.7%)</td>
<td>0.109</td>
</tr>
<tr>
<td>TVR</td>
<td>63 (10.4%)</td>
<td>47 (7.8%)</td>
<td>0.118</td>
</tr>
<tr>
<td>Cardiac death, MI, stroke</td>
<td>31 (5.1%)</td>
<td>16 (2.6%)</td>
<td>0.027</td>
</tr>
<tr>
<td>MACCE</td>
<td>92 (15.1%)</td>
<td>62 (10.3%)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

The rate of CV death, MI, stroke in ACS pts

TAPT vs. DAPT: 2.6% vs. 5.1%, OR 0.51

### Key Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Dual</th>
<th>Triple</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>events/total No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td>92/608 (15.1)</td>
<td>62/604 (10.3)</td>
<td>0.652 (0.408-0.907)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60/443 (13.5)</td>
<td>52/446 (11.7)</td>
<td>0.891 (0.607-1.307)</td>
</tr>
<tr>
<td>Female</td>
<td>32/165 (19.4)</td>
<td>10/158 (6.3)</td>
<td>0.275 (0.129-0.584)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>69/486 (14.2)</td>
<td>48/463 (10.4)</td>
<td>0.729 (0.501-1.063)</td>
</tr>
<tr>
<td>Yes</td>
<td>23/122 (18.9)</td>
<td>14/141 (9.9)</td>
<td>0.471 (0.230-0.964)</td>
</tr>
<tr>
<td><strong>Multivessel Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24/177 (13.5)</td>
<td>16/172 (9.3)</td>
<td>0.804 (0.414-1.561)</td>
</tr>
<tr>
<td>Yes</td>
<td>68/431 (15.8)</td>
<td>46/432 (10.7)</td>
<td>0.598 (0.407-0.877)</td>
</tr>
<tr>
<td><strong>Total Stent Length ≥ 30 mm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>43/286 (15.0)</td>
<td>31/288 (10.8)</td>
<td>0.688 (0.421-1.127)</td>
</tr>
<tr>
<td>Yes</td>
<td>49/322 (15.2)</td>
<td>31/316 (9.8)</td>
<td>0.612 (0.389-0.963)</td>
</tr>
<tr>
<td><strong>Stent Diameter ≤ 2.75 mm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>63/459 (13.7)</td>
<td>43/443 (9.9)</td>
<td>0.783 (0.501-1.088)</td>
</tr>
<tr>
<td>Yes</td>
<td>24/115 (20.9)</td>
<td>16/135 (11.9)</td>
<td>0.523 (0.273-1.003)</td>
</tr>
</tbody>
</table>

# One-year Major Side Effects

<table>
<thead>
<tr>
<th></th>
<th>DAPT (n=608)</th>
<th>TAPT (n=604)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>1 (0.2%)</td>
<td>0 (0%)</td>
<td>0.500</td>
</tr>
<tr>
<td>GI disorder</td>
<td>3 (0.5%)</td>
<td>2 (0.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Palpitation</td>
<td>2 (0.3%)</td>
<td>21 (3.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (0.5%)</td>
<td>17 (2.8%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Skin rash</td>
<td>5 (0.8%)</td>
<td>14 (2.3%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Discontinuation of Cilostazol</td>
<td>-</td>
<td>16 (2.6%)</td>
<td>-</td>
</tr>
</tbody>
</table>

Adding Cilostazol to DAPT Achieves Greater Platelet Inhibition than High-MD Clopidogrel in Patients with AMI

(Adjunctive Cilostazol versus high MD Clopidogrel in patients with AMI)

Young-Hoon Jeong,¹ Jin-Yong Hwang,¹ Younghwi Park,¹ Seok-Jae Hwang,¹ In-Suk Kim,¹ Choong Hwan Kwak,¹ Seung-Whan Lee,² Seong-Wook Park,² For the ACCEL-AMI Investigators

¹ Gyeongsang National University Hospital, Jinju, Korea.
² Asan Medical Center, Seoul, Korea.
Patients undergoing coronary stenting for AMI (n = 120)

**CLO 600mg loading → 75 mg/d before randomization**

- **Exclusion criteria (n = 25)**
  - Low LV ejection fraction,
  - anticoagulation etc.

- **Refusal (n = 5)**

**Randomization after pre-discharge platelet reactivity assessment (n = 90)**

- **Standard MD clopidogrel 75 mg/d (n = 30)**
  - Platelet reactivity after 30-day therapy (n = 30)

- **High MD clopidogrel 150 mg/d (n = 30)**
  - Platelet reactivity after 30-day therapy (n = 30)

- **Adjunctive cilostazol 100mg twice daily (n = 30)**
  - Platelet reactivity after 30-day therapy (n = 30)
Inhibition of maximal platelet aggregation (%)

- **Standard group**
- **High-MD group**
- **Triple group**

- **5 μmol/l ADP**
  - p = 0.002

- **20 μmol/l ADP**
  - p = 0.003

- p < 0.001 by ANOVA

- p < 0.001

- p < 0.001

- p < 0.001
Rate of HPPR (5 μmol/l ADP-based) (%)

**Baseline**
- p = 0.601
- p = 0.795
- p = 0.602 by ANOVA

**After 30-day therapy**
- p = 1.000
- p = 0.021
- p = 0.003 by ANOVA

**Summit TCT Asia Pacific 2009**

**TCT 2008**
3. ADP-induced platelet inhibition in patients with Complex lesion or DM?

High MD CLPD vs. TAPT: Enrollment was completed
4. ADP-induced platelet inhibition in patients with 2C19 polymorphism?

High MD CLPD vs. TAPT
Clopidogrel Response Variability: Change the Agent?


![Diagram of Clopidogrel metabolism and response variability.](image)
The impact of CYP450 Polymorphism in ACS pts on-clopidogrel

Substudy of TRITON-TIMI 38

2C19 mutant allele: Carrier vs. Non-Carrier

HR 1.53, 95% CI 1.07-2.19, P=0.01

HR 3.09, 95% CI 1.19-8.00, P=0.02

Risk of HPPR after CLPD LD 600mg
PREDICT score (n = 1092)

A

Points

Weighted PREDICT score

CYP2C19*2

B

Total points

Probability (high RPA >47%)

0.2 0.3 0.4 0.5 0.6 0.7 0.8

PREDICT score → Points → Probability of HPPR

1 = age > 65 yrs, ACS
2 = T2DM, CRF
3 = LV dysfunction
8 = one CYP2C19*2
14 = two CYP2C19*2

The **CYP2C19*2** and **CYP2C19*3** polymorphisms are associated with high post-clopidogrel platelet reactivity in acute myocardial infarction

Kim IS,* Jeong YH,† et al.

*Department of Laboratory Medicine,
†Division of Cardiology, Department of Internal Medicine,
Gyeongsang National University Hospital, Jinju

J Thromb Haemost 2009;E-pub.
# HPPR and Platelet Reactivity according to CYP2C19 genotyping

<table>
<thead>
<tr>
<th></th>
<th>Wild ((*1/*1) (n =57)</th>
<th>One mutant ((*1/*2, *1/*3) (n=59)</th>
<th>Two Mutant ((*2/*2, *2/*3) (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of HPPR</td>
<td>41.9%</td>
<td>58.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTA</td>
<td>43 ± 14 µmol/L</td>
<td>54 ± 15 µmol/L</td>
<td>62 ± 12 µmol/L</td>
<td>0.012</td>
</tr>
<tr>
<td>VerifyNow PRU % platelet inhibition</td>
<td>226 ± 90%</td>
<td>28 ± 23%</td>
<td>259 ± 74%</td>
<td>0.018</td>
</tr>
</tbody>
</table>

## Racial difference of CYP2C19 polymorphism

- Few CYP2C19*3 gene in whites
- Whites 20-30% vs. East Asian 55-65%

♣ Higher prevalence of HPPR in East Asian People?

**HPPR: 5µmol/L ADP induced MPA >50%**

J Thromb Haemost 2009; E-pub.
Variability of Platelet aggregation in chronic CLPD of 75mg/d (≥ 6 mo.)
East Asian patients with Coronary artery stent (n = 164)

- Up to 42% of pts taking Plavix® have suboptimal inhibition.

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How to overcome the effect of the loss-of-function 2C19 mutant allele?

1. High MD CLPD
2. Novel P2Y12 antagonist
3. Adjunctive cilostazol (TAPT)
Metabolic Pathway of Cilostazol

Cilostazol are mainly activated by CYP3A4/5 System

Potency of OPC 13015: X 3 of cilostazol

Potency of OPC 13213: X 1/3 of cilostazol

**Effect of High MD CLPD vs. TAPT according to CYP2C19 genotyping**

92 patients undergoing elective coronary stenting (preliminary data)

<table>
<thead>
<tr>
<th></th>
<th>High-MD CLPD (n = 13)</th>
<th>TAPT (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprocedural platelet reactivity</td>
<td>48.0 ± 18.2%</td>
<td>49.5 ± 16.5%</td>
<td>0.827</td>
</tr>
<tr>
<td>30-day Platelet reactivity</td>
<td>28.5 ± 13.1%</td>
<td>24.7 ± 15.4%</td>
<td>0.500</td>
</tr>
<tr>
<td>Δ platelet reactivity</td>
<td>19.5%</td>
<td>24.7%</td>
<td>0.432</td>
</tr>
<tr>
<td>30-day rate of HPPR</td>
<td>7.7%</td>
<td>6.7%</td>
<td>0.918</td>
</tr>
</tbody>
</table>

92 patients undergoing elective coronary stenting (preliminary data)

In non-carriers of CYP2C19 mutant allele (*1/*1), TAPT and high-MD CLPD significantly enhance inhibition of platelet reactivity and reduce the rate of HPPR.

- **Platelet reactivity**: 5μmol/l ADP-induced maximal platelet aggregation ($\text{Agg}_{\text{max}}$)
- **HPPR**: 5μmol/l ADP-induced $\text{Agg}_{\text{max}} > 50\%$
Effect of High MD CLPD vs. TAPT according to CYP2C19 genotyping

92 patients undergoing elective coronary stenting (preliminary data)

In carriers of CYP2C19 mutant allele, TAPT can and High-MD CLPD cannot overcome the effect of the loss-of-function CYP2C19 mutant allele.

TAPT achieves optimal platelet inhibition with lesser ischemic and bleeding events, especially in East Asian patients with a higher frequency of CYP2C19 Polymorphism.
Harmony
Endothelium
Platelet

The stronger is the better?
Pleiotropic Effects of Cilostazol

Cilostazol may give your patients RAINBOW against Atherosclerosis

Adjunctive Cilostazol to DAPT (TAPT)
Proven Efficacy and Safety in Pts with High Risk
(HPPR, ACS, CYP2C19 polymorphism and so on)

Neuroprotective Effect
Improvement of Lipid Metabolism
Inhibition of Inflammatory Cascade
Restoration of Endothelial Dysfunction
Reduction of Ischemia-Reperfusion Injury
Inhibition of Neointimal Hyperplasia after Stenting

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THE FINAL GOAL of APT:
PREVENT ISCHEMIA-AVOID BLEEDING

adapted from Gurbel PA et al. J Am Coll Cardiol. 2008;51:B86