The Role of Triple Antiplatelet Therapy in Patients with High Risk

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Metabolic Pathways blocked By Statins

Statins

Acetyl-CoA + Acetoacetyl-CoA → HMG-CoA → Mevalonate → Isopentenyl PP → Geranyl PP → Farnesyl PP

Early/Rapid and Later Benefit  (pleiotropic effect)
Important in Vascular Cellular Responses

Prenylation

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

Cilostazol

5'AMP

PDE3A

Adenosine

A1

A2

ATP

cAMP

Platelet

Endothelial cell

Smooth muscle cell

Cardiocyte

Targets

<table>
<thead>
<tr>
<th>cAMP actions (selected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inhibition of aggregation</td>
</tr>
<tr>
<td>• Inhibition of expression of adhesion molecules</td>
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<tr>
<td>• Inhibition of expression of adhesion molecules</td>
</tr>
<tr>
<td>• Angiogenesis</td>
</tr>
<tr>
<td>• Vasodilatory action</td>
</tr>
<tr>
<td>• Inhibition of proliferation, migration and matrix synthesis</td>
</tr>
<tr>
<td>• Headache</td>
</tr>
<tr>
<td>• Palpitation</td>
</tr>
<tr>
<td>• Tachycardia</td>
</tr>
</tbody>
</table>

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Role of cAMP / Protein Kinase A

- PKA can phosphorylate many different proteins depending on tissue type and status.
- PKA can activate enzymes or gene regulatory proteins.

Inactive protein kinase A (PKA)
- Regulatory subunit of PKA binds cAMP
- Regulatory subunit dissociates from the catalytic subunit
- Free PKA catalytic subunit migrates to nucleus
- PKA catalytic subunit phosphorylates CREB* and activates transcription

Altered Protein Function
- Altered Gene Expression
- Altered Protein Function

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Pleiotropic Effects of Cilostazol


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

• Restoration of Endothelial dysfunction
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• 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
Antiplatelet Therapy in ACS & PCI

DAPT is the standard therapy

• 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.

Inhibition of Platelet Aggregation (%)

- ADP: 5 μM
  - Aspirin: 46.5%
  - Clopidogrel: 54.2%
  - Cilostazol: 55.2%
- Collagen: 2 μg/ml
  - Aspirin: 15.2%
  - Clopidogrel: 36.9%
  - Cilostazol: P<0.01
- Epinephrine: 10 μM
  - Aspirin: 48%
  - Clopidogrel: 36.9%
  - Cilostazol: 42.9%
- Arachidonic acid: 200 μg/ml
  - Aspirin: P=NS
  - Clopidogrel: P=NS
  - Cilostazol: P=NS

Cilostazol vs Clopidogrel Therapy After BMS Implantation


* AMI were due to stent thrombosis

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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)


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## Safety of triple antiplatelet therapy

<table>
<thead>
<tr>
<th></th>
<th>DAPT (n=1597)</th>
<th>TAPT (n=1415)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</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>Adverse side effect</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.

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

*Primary Endpoint*

P2Y$_{12}$ 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 Aggmax > 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

Rate of HPPR
(5 μmol/L ADP-induced Agg\textsubscript{max} > 50%)


Baseline After 30-days therapy

Rate of HPPR
(5 μmol/L ADP-induced Agg\textsubscript{max} > 50%)

High MD group
Triple group

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

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.

Adjunctive Cilostazol reduces the rate of HPPR & intensifies platelet inhibition as compared with high-MD clopidogrel

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>Outcome</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 events/total No. (%)</th>
<th>Triple events/total No. (%)</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients</strong></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>( \rho )</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)

High MD clopidogrel 150 mg/d (n = 30)

Adjunctive cilostazol 100mg twice daily (n = 30)

Platelet reactivity after 30-day therapy (n = 30)
Inhibition of maximal platelet aggregation (%)

- 5 μmol/l ADP
  - Standard group: p = 0.002
  - High-MD group: p < 0.001
  - Triple group: p < 0.001

- 20 μmol/l ADP
  - Standard group: p < 0.001
  - High-MD group: p < 0.001
  - Triple group: p < 0.001

ANOVA
Rate of HPPR (5 μmol/l ADP-based) (%)

Baseline

After 30-day therapy

p = 0.602 by ANOVA

p = 0.601

p = 0.795

p = 1.000

p = 0.532

p = 0.003 by ANOVA

p = 0.003

p = 0.021
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?


**Pro-drug**

**Hydrolysis**

**Oxidation**

(Cytochrome P450)

**Esterases (hCE1)**

(85-90% Inactive Metabolites)

**Esterases (hCE2)**

**R-95913 (Thiolactone)**

**R-138727**
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)

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

PREDICT score → Points → Probability of HPPR

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>
</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%

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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</th>
<th>TAPT</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>

Non-carrier of CYP2C19 mutant allele (*1/*1)

In non-carriers of CYP2C19 mutant allele, 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 (Agg_max)
HPPR: 5μmol/l ADP-induced Agg_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.
The stronger is the better?

Harmony

Endothelium

Platelet
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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Thank You for Your Attention
THE FINAL GOAL of APT:
PREVENT ISCHEMIA-AVOID BLEEDING

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