Limits of Platelet-Oriented Treatment:
“Cilostazol” as Multidisciplinary Approach

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## Disclosures

<table>
<thead>
<tr>
<th>Research Grants/Support</th>
<th>Honoraria/Consulting</th>
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<tbody>
<tr>
<td>Dong-A Pharmaceutical</td>
<td>Otsuka</td>
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<tr>
<td>Boehringer-Ingelheim</td>
<td>Sanofi-Aventis</td>
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<tr>
<td>Otsuka</td>
<td>Daiichi Sankyo Inc</td>
</tr>
<tr>
<td>Accumetrics</td>
<td>Nanosphere</td>
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<tr>
<td>Multiplate</td>
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</tbody>
</table>
Consensus and Future Directions on the Definition of High On-Treatment Platelet Reactivity to Adenosine Diphosphate

Laurent Bonello, MD,* Udaya S. Tantry, PhD, §§ Rossella Marcucci, MD, PhD, ||| Ruediger Blindt, MD, # Dominick J. Angiolillo, MD, PhD, ||| Richard Becker, MD, ¶¶ Deepak L. Bhatt, MD, MPH, # Marco Cattaneo, MD, ¶ Jean Philippe Collet, MD, PhD, † Thomas Cuisset, MD, † Christian Gachet, MD, PhD, § Gilles Montalescot, MD, PhD, † Lisa K. Jennings, PhD, *** Dean Kereiakes, MD, †† Dirk Sibbing, MD, ** Dietmar Trenk, PhD, †† Jochem W. Van Werkum, MD, PhD, ‡ Franck Paganelli, MD,* Matthew J. Price, MD, ††‡ Ron Waksman, MD, §§§ Paul A. Gurbel, MD, §§ for the Working Group on High On-Treatment Platelet Reactivity

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Available methods for testing...

Laboratory-based methods

Methods allowing near-patient testing

LTA

VerifyNow

Whole blood test

VASP

Multiplate (MEA)

Platelet-oriented method

Most promising for implementation into clinical routine
Personalized Antiplatelet Therapy

Recent data suggest that ischemic risk increases rapidly above “a critical level of platelet reactivity”

“High on-treatment platelet reactivity (HPR)”

The criteria of HPR

1) 5 µM ADP-PA > 46%  
   20 µM ADP-PA > 59%
2) PRU > 235 (VerifyNow)
3) PRI > 50% (VASP)
4) Multiplate > 468 AU

Bonello et al. J Am Coll Cardiol 2010;56:919-33
Available Strategies of P2Y$_{12}$ Inhibition

Therapeutic profile not affected by CYP, ABCB1 genetic variation

TRITON-TIMI 38 Study: Prasugrel vs. Standard Clopidogrel

14.5 months CV death, Nonfatal MI and Nonfatal Stroke

- **HR 0.81 (0.73-0.90)**
- **P < 0.001**

**NNT = 46 (1<sup>st</sup> endpt.)**
**NNH = 167 (Bleeding)**

Reduced MD- 5mg
Guided by PK (n=1159)
Age≥75 yr (n=121) ↑19%
or Wt <60 kg (n=46) ↑40%

TIMI Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Non-CABG</td>
<td>2.4%</td>
<td>1.8%</td>
<td>0.03</td>
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<tr>
<td>Major or Minor</td>
<td>4.0%</td>
<td>3.0%</td>
<td>&lt;0.001</td>
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<tr>
<td>CABG-related</td>
<td>13.4%</td>
<td>3.2%</td>
<td>&lt;0.001</td>
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</table>

PLATO Trial: Clopidogrel vs. Ticagrelor in ACS Patients

UA / NSTEMI (moderate-high risk), STEMI (if primary PCI, n=8340)
All receiving ASA; clopidogrel-treated or -naïve;
randomized within 24 h of index event

Clopidogrel
300 mg LD+ 75 mg/d;
(additional 300 mg allowed pre PCI)

Ticagrelor
180 mg LD+ 90 mg/bd;
(additional 90 mg pre-PCI)

12-month maximum exposure (Minimum 6 months exposure of last included pt)

Clopidogrel Loading Dose
~46% got clopidogrel before randomization
(≥ 600mg = 19.6%)

In 1000 ACS patients, replacing clopidogrel with ticagrelor for 12 months,
- 14 fewer deaths
- 11 fewer MI
- 6-8 fewer cases of ST
- no increase in bleeding requiring ransfuson.

Primary Outcome- CV death + MI + stroke

NNT = 53 (1st endpt.)
NNT = 91 (CV death)
NNT = 91 (MI)

HR 0.84 (95% CI 0.77–0.92), p=0.0003

Balancing Safety and Efficacy

High risk of ischemic events

“Sweet spot” Therapeutic Zone

High risk of bleeding events

HPR LPR

Inhibition of platelet aggregation

Risk of any event

Ischemic risk

Bleeding risk

How much **enthusiasm** is needed to control platelet activation?
“Philosophy of Today” will make Creativity in Tomorrow.
Modern Times = Absence of Philosophy

Leonardo da Vinci
(invention based on philosophy)
“Platelet Research”: Absence of Philosophy

A Case of Enthusiasm Exceeding the Evidence/Philosophy

Enthusiasm

Evidence/Philosophy
Paradox in “Platelet Research”

- “Smoking” paradox
- “Female” paradox
- “Old age” paradox
- “DM” paradox
- “CKD” paradox
- “Asian” paradox
- …
Paradox in “Platelet Research”

- “Smoking” paradox
- “Female” paradox
- “Old age” paradox
- “DM” paradox
- “CKD” paradox
- “Asian” paradox
- ...
**Platelet Reactivity in Korean AMI pts**
(First report of ADP-stimulated platelet reactivity in East Asians)

Clopidogrel 600mg LD, followed by 75 mg/d

<table>
<thead>
<tr>
<th>CYP2C19 SNP</th>
<th>0 LoF allele (n = 57)</th>
<th>1 LoF allele (n = 59)</th>
<th>2 LoF alleles (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of HPR</td>
<td>18 (31.6%)</td>
<td>33 (55.9%)</td>
<td>12 (65.0%)</td>
<td>0.002</td>
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<tr>
<td>LTA, %</td>
<td></td>
<td></td>
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<tr>
<td>5 µM ADP-PA</td>
<td>43±14</td>
<td>49±14</td>
<td>52±17</td>
<td>0.012</td>
</tr>
<tr>
<td>20 µM ADP-PA</td>
<td>54±15</td>
<td>62±12</td>
<td>64±15</td>
<td>0.002</td>
</tr>
<tr>
<td>VerifyNow PRU</td>
<td>226±90</td>
<td>259±74</td>
<td>284±84</td>
<td>0.018</td>
</tr>
</tbody>
</table>

**HPR (5 µM ADP-PA > 46%): 47.1%**

GNUH ACCEL registry

**PD profile:** Korean patients undergoing elective PCI

(n = 466: at least 12 hours after 600mg clopidogrel LD)

**HPR:**

- 43.3%
- 59.4%
- 63.5%

**High prevalence of HPR:**

High frequency of CYP2C19 LoF allele

(East Asians: Caucasian = 60-70%; 25-30%)

Racial Difference in CV death/MI/stroke among Pts on Antiplatelet Therapy

GUSTO Mod bleed HR
3.78 (1.35-1.60)
1.46 (0.63-3.36)
1.00 (Reference)
3.15 (1.09-9.11)

Racial difference of Stent Thrombosis: Asian vs. Western Population

Similar ST incidence of Asian Registry to RCT Results, but lower to Western Registry.
What’s the magic in Asians?

VS.

[Image of two women sitting back to back] vs. [Image of a woman in a stylish outfit]
Development of Arterial Thrombi

Procoagulant forces

- Platelet-activating factor
- Endothelin 1
- Thromboxane A2
- Tissue factor
- Tissue-factor-bearing microparticles
- Clotting factors
- Von Willebrand factor
- Plasminogen activator inhibitor 1
- α2-plasmin inhibitor
- Carboxypeptidase B2
- Others...

Anticoagulant forces

- Prostacyclin
- Nitric oxide
- Carbon monoxide
- Antithrombin
- Protein C/protein S/thrombomodulin system
- Tissue factor pathway inhibitor
- Tissue-type plasminogen activator
- Urokinase-type plasminogen activator
- Others...

Plausible Mechanism of Atherothrombosis

- **Progenitor cell**
- **Endothelial dysfunction** (e.g. adhesion molecule: vWF)
- **Obesity**
- **Oxidative stress**
- **Inflammation** (e.g. monocyte, CRP)
- **Shearing force**
- **Lipid particle** (e.g. oxidized LDL, HDL)

**Gene-environment interaction (RACE)**

- **Platelet activation**
  - **Procoagulant activity** (e.g. TF-Thrombin-Fibrin)
- **Fibrinolytic activity**

**Gene**

**Environment**

**Interaction**

**RACE**
Racial Difference in ICH Risk among AF Pts on Warfarin (18867 pts admitted to Kaiser Permanente Southern California)

<table>
<thead>
<tr>
<th>Race</th>
<th>ICH risk</th>
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</thead>
<tbody>
<tr>
<td>White (n=14809)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Black (n=1534)</td>
<td>2.04 (1.25 – 3.35)</td>
</tr>
<tr>
<td>Hispanic (n=1798)</td>
<td>2.06 (1.31 – 3.24)</td>
</tr>
<tr>
<td>Asian (n=726)</td>
<td>4.06 (2.47 – 6.65)</td>
</tr>
</tbody>
</table>

Effect of age on the incidence of VTE among different racial/ethnic groups

Theoretical Reason for Racial Difference in VTE

Ethnic Difference in CRP level

A cross-sectional analysis of 3154 women, without known CVD and hormone therapy (SWAN study)

Multicenter Randomized Trial Evaluating Efficacy of Cilostazol on Platelet reactivity, Inflammation, and Myonecrosis in ACS Patients

Young-Hoon Jeong, MD, PhD
On behalf of the ACCEL-LOADING-ACS Investigators

Gyeongsang National University Hospital, Jinju, Korea;
Sinai Center for Thrombosis Research, Baltimore, MD, USA.

ClinicalTrials.gov Identifier: NCT01354808
Relationship between VerifyNow and 30-day MACE

**ROC curve analysis**

<table>
<thead>
<tr>
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<th>PRU</th>
<th>BASE</th>
<th>PI</th>
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<tbody>
<tr>
<td><strong>AUC</strong></td>
<td>0.583</td>
<td>0.516</td>
<td>0.649</td>
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<tr>
<td><strong>Cutoff</strong></td>
<td>&gt;288</td>
<td>≤293</td>
<td>≤12%</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>47.3%</td>
<td>52.7%</td>
<td>74.6%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>70.8%</td>
<td>59.9%</td>
<td>57.1%</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>37.7%</td>
<td>33.0%</td>
<td>39.4%</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td>78.2%</td>
<td>77.2%</td>
<td>85.7%</td>
</tr>
<tr>
<td><strong>+LR</strong></td>
<td>1.62</td>
<td>1.62</td>
<td>1.74</td>
</tr>
<tr>
<td><strong>-LR</strong></td>
<td>0.75</td>
<td>0.75</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
<td>64.2%</td>
<td>57.9%</td>
<td>62.0%</td>
</tr>
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</table>

![ROC curve diagram](image)
30-day MACE in PCI-treated ACS patients according to Combined VerifyNow and CRP

Log rank $P < 0.001$

ACCEL-LOADING-ACS.
Asians may have low “thrombogenicity”
Balancing Safety and Efficacy in East Asians

Shift to left side

Platelet activation may be protected from other mechanisms.

High risk of ischemic events

“Sweet spot”

High risk of bleeding events

Inhibition of platelet aggregation
“Cilostazol” as Multidisciplinary Approach
Role of Phosphodiesterases (PDEs) and Inhibitors

↑ cAMP and cGMP → ↑ protein kinase → phosphorylation of specific substrates

<table>
<thead>
<tr>
<th>Family</th>
<th>Substrate</th>
<th>Tissue expression</th>
<th>Inhibitors</th>
<th>Disease targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE1</td>
<td>cGMP &gt; cAMP</td>
<td>Heart, vascular smooth muscle and brain</td>
<td>Vinpocetin, IC86340</td>
<td>Cerebrovascular disorders and age-related memory impairment, cardiac hypertrophy</td>
</tr>
<tr>
<td>PDE2</td>
<td>cGMP = cAMP</td>
<td>Platelets, heart and endothelial cells</td>
<td>EHNA, EHNA analogues, BAY 60-7550, PDP</td>
<td>Memory impairment, endothelial permeability in inflammatory conditions</td>
</tr>
<tr>
<td>PDE3</td>
<td>cAMP &gt; cGMP</td>
<td>Platelets, vascular smooth muscle, corpus cavernosum and heart</td>
<td>Clostazol, milrinone, vesnarinone, iloprost, anagrelide</td>
<td>Peripheral vascular disease, congestive heart failure, airways disease, fertility, ischaemic cardiovascular disease</td>
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<tr>
<td>PDE4</td>
<td>cAMP</td>
<td>Lung, heart, vascular smooth muscle, brain, inflammatory and immune cells</td>
<td>Rolipram, etazolate, zardaverine</td>
<td>Chronic obstructive pulmonary disease, asthma, allergic disease</td>
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<tr>
<td>PDE5</td>
<td>cGMP</td>
<td>Platelets, vascular smooth muscle and corpus cavernosum</td>
<td>Sildenafil, vardenafil, tadafil, zaprinast, dyopirdamole</td>
<td>Erectile dysfunction, ischaemic cardiovascular disease</td>
</tr>
<tr>
<td>PDE6</td>
<td>cGMP &gt; cAMP</td>
<td>Retinal rods and cones</td>
<td>Sildenafil, zaprinast, dyopirdamole</td>
<td>None</td>
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<tr>
<td>PDE7</td>
<td>cAMP &gt; cGMP</td>
<td>T cell, B cell, skeletal muscle and heart</td>
<td>BRL 50481, IC245, dyopirdamole</td>
<td>Inflammation, osteoporosis</td>
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<tr>
<td>PDE8</td>
<td>cAMP</td>
<td>Testis, eye, liver, kidney, skeletal muscle, embryo, ovary and brain</td>
<td>Zaprinast</td>
<td>None</td>
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<tr>
<td>PDE9</td>
<td>cGMP</td>
<td>Brain, small intestinal smooth muscle, liver, kidney, lung, testis, skeletal muscle and heart</td>
<td>BAY 73-6691</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>PDE10</td>
<td>cAMP &gt; cGMP</td>
<td>Testis and brain</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>PDE11</td>
<td>cAMP = cGMP</td>
<td>Skeletal muscle, prostate, kidney, liver, pituitary, salivary glands and testis</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Pharmacokinetics and Pharmacodynamics of Cilostazol

6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone

• **Mechanism:**
  - Inhibition of PDE3 (platelets, VSMC, heart, and adipocytes) $\rightarrow$ ↑ cAMP
  - Inhibition of adenosine uptake (erythrocytes, platelets, muscle cells, and endothelial cells) $\rightarrow$ ↑ adenosine

• **Metabolism:** Extensively metabolized by liver excreted by urine (74%) and feces (20%)
  - pathway: OPC-13015 (CYP3A4)
  - OPC-13213 (CYP3A5 and 2C19)

• Max. concentration: 3~3.65 hours
• Max. platelet inhibition: ~6 hours

Cilostazol: old drug, but new mechanism

<table>
<thead>
<tr>
<th>Effect</th>
<th>PDE3-dependent (cAMP)</th>
<th>PDE3-independent</th>
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</thead>
<tbody>
<tr>
<td>Antiplatelet effect</td>
<td>O</td>
<td>O (adenosine)</td>
</tr>
<tr>
<td>Vasodilatory effect (VSMC relaxation)</td>
<td>O</td>
<td>O (adenosine)</td>
</tr>
<tr>
<td>Antiproliferative effect</td>
<td>O</td>
<td>O (adenosine)</td>
</tr>
<tr>
<td>(control of VSMC proliferation and migration)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on endothelial dysfunction</td>
<td>Δ</td>
<td>Δ (PGE₁, PGI₂, Sirt 1)</td>
</tr>
<tr>
<td>(NO release)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiatherogenic effect</td>
<td>Δ</td>
<td>-</td>
</tr>
<tr>
<td>(↓ adhesion molecule, ↓ inflammatory cells and cytokines)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control of dyslipidemia</td>
<td>Δ (lipoprotein lipase)</td>
<td>-</td>
</tr>
<tr>
<td>(↓ triglyceride, ↑ HDL-cholesterol and apolipoprotein A₁)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protection against ischemia/reperfusion injury</td>
<td>-</td>
<td>Δ (adenosine)</td>
</tr>
<tr>
<td>(PI3/Akt pathway)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive chronotropic effect</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>Negative chronotropic effect</td>
<td>-</td>
<td>Δ (adenosine)</td>
</tr>
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</table>

Initiation of Platelet Aggregation

GP IIb/IIIa receptor activation

Shape change

Ca\(^{2+}\) flux

P2X\(_1\)

P2Y\(_1\)

P2Y\(_2\)

ADP

Ca\(^{2+}\) mobilization

PLC\(\beta\)

PLC\(\gamma\)

PKC

G\(_q\)

G\(_{i2}\)

"Rho"

Shape change

IP3 + DAG

IP3

PIP2

MLCK-P

Granule secretion

GP IIb/IIIa receptor activation

Stabilization of Platelet Aggregation

cAMP

VASP

PKA

VASP-P

GP IIb/IIIa receptor activation

Prostacyclin

Angiolillo DJ et al JACC 2007

Hepatic CYP Biotransformation

85% inactive metabolites (Esterases in blood)

Gastro-intestinal absorption

Clopixol

15% active metabolite

Gastro-intestinal absorption

Hepatic CYP Biotransformation

85% inactive metabolites (Esterases in blood)

Gastro-intestinal absorption

Hepatic CYP Biotransformation

85% inactive metabolites (Esterases in blood)

Gastro-intestinal absorption

Hepatic CYP Biotransformation

85% inactive metabolites (Esterases in blood)
Less Bleeding Tendency of Cilostazol

- **Bleeding time of APT**


  ![Bleeding Time Graph]

- **Endothelium-targeted antithrombotic therapy**

- **Relatively short recovery time of platelet function**
Antiplatelet and Vasodilation of Cilostazol

- Peripheral artery disease: FDA approved
- Secondary prevention of Cerebral infarction: more benefit than aspirin

Primary endpoint
3.71% vs. 2.76%

Safety endpoint
1.78% vs. 0.77%

**Effect of Cilostazol on Dyslipidemia**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>No of patients</th>
<th>Dose mg (daily)</th>
<th>Duration (weeks)</th>
<th>Effect (%)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Triglycerides</td>
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<tr>
<td>Dawson et al. [7]</td>
<td>1998</td>
<td>52</td>
<td>200</td>
<td>2</td>
<td>-24</td>
<td>NS</td>
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<td></td>
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<td>50</td>
<td></td>
<td>4</td>
<td>-31</td>
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<td>8</td>
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<td>Elam et al. [8]</td>
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<td>12</td>
<td>-25</td>
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<tr>
<td>Lee et al. [12]</td>
<td>2001</td>
<td>95</td>
<td>200</td>
<td>12</td>
<td>-15</td>
<td>&lt; 0.001</td>
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<td>Nakamura et al. [9]</td>
<td>2003</td>
<td>17</td>
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<td>Wang et al. [10]</td>
<td>2003</td>
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<td>24</td>
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<td>Samra et al. [13]</td>
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<td>O’Donnell et al. [11]</td>
<td>2009</td>
<td>39</td>
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<tr>
<td>Nakamura et al. [9]</td>
<td>2003</td>
<td>17</td>
<td>200</td>
<td>24</td>
<td>+4</td>
<td>NS</td>
</tr>
<tr>
<td>Wang et al. [10]</td>
<td>2003</td>
<td>56</td>
<td>200</td>
<td>24</td>
<td>+17</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Samra et al. [13]</td>
<td>2003</td>
<td>123</td>
<td>100/200</td>
<td>12</td>
<td>+20</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>O’Donnell et al. [11]</td>
<td>2009</td>
<td>39</td>
<td>200</td>
<td>6</td>
<td>+7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24</td>
<td>+14</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Antiatherogenic Effect of Cilostazol

**Progression of maximal carotid intima-media thickness (mm) (Metaanalysis: n = 698)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cilostazol</th>
<th>Control</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>1.16.1 16 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ahn CW 2011</td>
<td>-0.06</td>
<td>0.04</td>
<td>60</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.49 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.16.2 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ahn CW 2011</td>
<td>-0.01</td>
<td>0.04</td>
<td>60</td>
</tr>
<tr>
<td>DAPC 2010</td>
<td>-0.59</td>
<td>0.24</td>
<td>145</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>205</td>
<td></td>
<td>212</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Ch^2 = 0.42, df = 1 (P = 0.52); P = 0%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 5.80 (P &lt; 0.00001)</td>
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</tr>
<tr>
<td>1.16.3 2 years</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ahn CM 2010</td>
<td>0.02</td>
<td>0.43</td>
<td>64</td>
</tr>
<tr>
<td>DAPC 2010</td>
<td>-0.08</td>
<td>0.26</td>
<td>145</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>209</td>
<td></td>
<td>218</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Ch^2 = 0.33, df = 1 (P = 0.87); P = 0%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.21 (P &lt; 0.00001)</td>
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<tr>
<td>1.16.4 ≥2.6 years</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mitsuhashi N 2004</td>
<td>0.04</td>
<td>0.02</td>
<td>31</td>
</tr>
<tr>
<td>Shindo-Tagawa T 2002</td>
<td>0.2</td>
<td>0.17</td>
<td>43</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>74</td>
<td></td>
<td>77</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Ch^2 = 3.43, df = 1 (P = 0.06); P = 71%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 2.67 (P = 0.008)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>548</td>
<td>567</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Ch^2 = 25.26, df = 6 (P = 0.0003); P = 76%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.28 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Ch^2 = 16.72, df = 3 (P = 0.0006); P = 82.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Unproven effect of cilostazol on CAD plaque progression**

Effect of Cilostazol on Inflammation

High-sensitivity CRP (mg/L) in Type 2 DM patients with PAOD (n = 192)

Before Treatment

After Treatment (6 month)

$P = \text{NS}$

$P < 0.001$

Cilostazol group (n=92)
Placebo group (n=100)

“ACCEL” series: searching for cilostazol’s secret

- ACCEL-RESISTANCE (J Am Coll Cardiol)
- ACCEL-AMI (Circ Cardiovasc Interv)
- ACCEL-COMPLEX (Thromb Haemost)
- ACCEL-DM (Diabetes Care)
- ACCEL-POLYMORPHISM (Circ Cardiovasc Interv)
- ACCEL-AMI2C19 (JACC Cardiovasc Interv)
- ACCEL-DOUBLE (JACC Cardiovasc Interv)
- ACCEL-TRIPLE (Br J Clin Pharmacol)
- ACCEL-SWITCH (J Thromb Haemost)
- ACCEL-DOUBLE-2N3 (Eur Heart J: in submission)
- ACCEL-PPI (ACC 2012)
- ACCEL-LOADING-ACS (TCTAP 2012 LBCT session)
- ACCEL-HPR (on writing)
- ACCEL-PARAZOL (on writing)
- ACCEL-EPISODE (on going)
**Adjunctive Cilostazol vs. high-MD Clopidogrel in HPR (ACCEL-RESISTANCE study)**

*High On-Tx Platelet Reactivity (HPR) : 5 μM ADP-induced PA > 50%

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

\[
\begin{align*}
\text{Inhibition of maximal platelet aggregation (%)} &:& \text{p} < 0.001 \\
5 \mu\text{mol/L ADP} &:& 51.1 \pm 23 \\
20 \mu\text{mol/L ADP} &:& 39.6 \pm 23
\end{align*}
\]

Percent change of PRU

\[ p = 0.022 \]

Inhibition of PRU (%)

- **High MD group**: \( 23.1 \pm 30 \)
- **Triple group**: \( 39.6 \pm 24 \)

Rate of HPR
(5 μM ADP-induced PA > 50%)

Pre-procedure: 26.7%
30-day follow-up: 3.3%

p = 0.012

“ACCEL” series: searching for cilostazol’s secret

- ACCEL-RESISTANCE: Clopidogrel nonresponsiveness
- ACCEL-AMI: AMI patients
- ACCEL-COMPLEX: Complex PCI
- ACCEL-DM: Diabetes patients
- ACCEL-POLYMORPHISM: CYP2C19 polymorphism
- ACCEL-AMI2C19: CYP2C19 polymorphism
- ACCEL-PPI: proton pump inhibitor

Proven efficacy of adjunctive cilostazol to DAPT

- HPR
- AMI
- DM
- Complex PCI
- CYP2C19 polymorphism
- Proton pump inhibitor
Postulated Disease Activity in East Asians

- Procoagulant activity
- Platelet activation
- Inflammation

Early
Late
Very Late

TAPT
DAPT (ASP + cilo/clop)
Mono-therapy (ASP vs. clop vs. cilo)
CIDES Trial
(Cilostazol for Diabetic Patients in DES)

280 DM patients undergoing elective PCI:
Aspirin+ Clopidogrel + Cilostazol for 1 mo.

- Clopidogrel 75 mg/d for 5 mo. (n = 139)
- Cilostazol 100 mg bid for 5 mo. (n = 141)

- Primary end point: MLD at 6 mo.
- Secondary end point: mean %DS, ISR, MACE

Clinical events at 6 months

- **Cilostazol**
- **Clopidogrel**

PD Effect of Clopidogrel vs. Cilostazol in DES-treated patients

CYP2C19 LoF allele carriers

PK of Shorting-acting vs. Slow-release Cilostazol

\[ C_{\text{max}} 109\%, \ AUC \ 92\% \]

God did not want to use “the same language”

God might want “multidisciplinary approach” and “race-based antithrombotic treatment”