Effect of Cilostazol on Primary and Secondary Prevention of Atherosclerotic Cardiovascular Disease in Korean Patients with type 2 DM

Department of Endocrinology and Metabolism, Kyung Hee University School of Medicine

Sang Youl Rhee M.D., Ph.D.
Introduction
Type 2 diabetes is associated with Serious Complications

**Diabetic Retinopathy**
Leading cause of blindness in adults

**Diabetic Nephropathy**
Leading cause of end-stage renal disease

**Stroke**
2- to 4-fold increase in cardiovascular mortality and stroke

**Cardiovascular Disease**
8/10 individuals with diabetes die from CV events

**Diabetic Neuropathy**
Leading cause of non-traumatic lower extremity amputations

---

VI. PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS, p. S27

A. Cardiovascular disease
   1. Hypertension/blood pressure control
   2. Dyslipidemia/lipid management
   3. Antiplatelet agents
   4. Smoking cessation
   5. Coronary heart disease screening and treatment
Significant overlap in “traditional risk factors” among those with or without CHD

Framingham Heart Study: 26-year follow-up

35% of CHD occurs in people with total chol. < 200 mg/dl (< 5.2 mmol/l)

LDL cholesterol distribution

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>HDL - Cholesterol (mg/dL)</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>220</td>
<td></td>
</tr>
<tr>
<td>Treatment for Hypertension</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Note:** These estimates may underestimate the 10-year and lifetime risk for persons from some race/ethnic groups, especially American Indians, some Asian Americans (e.g., of south Asian ancestry), and some Hispanics (e.g., Puerto Ricans), and may overestimate the risk for others, including some Asian Americans (e.g., of east Asian ancestry) and some Hispanics (e.g., Mexican Americans).

Because the primary use of these risk estimates is to facilitate the very important discussion regarding risk reduction through lifestyle change, the imprecision introduced is small enough to justify proceeding with lifestyle change counseling informed by these results.

---

*Intended for use if there is not ASCVD and the LDL-cholesterol is < 190 mg/dL.

**Optimal risk factors include: Total cholesterol of 170 mg/dL, HDL-cholesterol of 50 mg/dL, Systolic BP of 110 mm Hg, Not taking medications for hypertension, Not a diabetic, Not a smoker.
Screening for novel CV risk factors & subclinical atherosclerosis

Numerous Risk Factors:
- High LDL
- Low HDL
- High BP
- Diabetes
- Smoking
- CRP
- Metabolic Syn
- Lp(a)
- Homocysteine
- Dense LDL
- Lp-PLA2
- ApoB/ApoA
- Family History
- Sedentary Life
- Obesity
- Stress
- ...
- ?

Over 200 risk factors have been reported.

Examples of Arterial Structure Tests:
- Carotid IMT and Plaque Measured by Ultrasound
- Aortic and Carotid Plaque Detected by MRI
- Coronary Calcium Score Measured by CT
- Ankle Brachial Index
- Brachial Vasoreactivity Measured by Ultrasound
- Vascular Compliance Measured by Radial Tonometry
- Microvascular Reactivity Measured by Fingertip Tonometry
An increased IMT was defined as an IMT greater than the mean healthy subject value, +1S.D (≈ 0.82-0.84mm)
Table 3  Regression coefficients (β) and HRs of the simplified Cox proportional hazard model for 5-year risk of ICVD, and translation of β into total burden score

<table>
<thead>
<tr>
<th>Variables in the model</th>
<th>N</th>
<th>β</th>
<th>HR (95% CI)</th>
<th>Total burden score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional risk score (per 1 score increase)</td>
<td>1734</td>
<td>0.274</td>
<td>1.32 (1.24 to 1.41)</td>
<td>1 (Ref)</td>
</tr>
<tr>
<td>Combined carotid atherosclerosis categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No plaque and IMT&lt;0.63 mm</td>
<td>255</td>
<td>Ref</td>
<td>1.00</td>
<td>0</td>
</tr>
<tr>
<td>No plaque and 0.63≤IMT≤0.68 mm</td>
<td>285</td>
<td>0.271</td>
<td>1.31 (0.38 to 4.50)</td>
<td>1</td>
</tr>
<tr>
<td>No plaque and 0.69≤IMT≤0.74 mm</td>
<td>234</td>
<td>0.510</td>
<td>1.67 (0.50 to 5.59)</td>
<td>2</td>
</tr>
<tr>
<td>No plaque and IMT≥0.75 mm</td>
<td>269</td>
<td>0.786</td>
<td>2.19 (0.69 to 7.02)</td>
<td>3</td>
</tr>
<tr>
<td>1 segment with plaque</td>
<td>380</td>
<td>0.834</td>
<td>2.30 (0.85 to 5.73)</td>
<td>3</td>
</tr>
<tr>
<td>2 segments with plaque</td>
<td>203</td>
<td>1.263</td>
<td>3.54 (1.12 to 11.14)</td>
<td>5</td>
</tr>
<tr>
<td>≥3 segments with plaque</td>
<td>108</td>
<td>1.785</td>
<td>5.96 (1.86 to 19.13)</td>
<td>7</td>
</tr>
</tbody>
</table>

ICVD, ischaemic cardiovascular disease; IMT, intima-media thickness.

Wuxiang Xie et al., Heart 2011;97:1326-1331
Behavioral change

Smokers with plaque were 6-fold more likely to quit smoking

- Lausanne, Switzerland
- Randomized trial in smokers
  - N=153
  - Counseling ± imaging
  - Absolute 22.2% quit rate
  - NNT 6

Changes in physician management after CIMT screening

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Presence of advanced subclinical atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
</tr>
<tr>
<td>Add aspirin</td>
<td>6.59</td>
</tr>
<tr>
<td>Add blood pressure medication</td>
<td>4.02</td>
</tr>
<tr>
<td>Add lipid-lowering medication</td>
<td>5.36</td>
</tr>
<tr>
<td>Refer for additional tests</td>
<td>1.26</td>
</tr>
</tbody>
</table>

Cilostazol: Clinical evidences
Cilostazol

- **Antiplatelet, vasodilator properties**
  - Phosphodiesterase-3 inhibitor

- **Indication**
  - Intermittent claudication: 100 mg bid
  - PCI: 100 mg bid (+ aspirin or clopidogrel)
  - Secondary prevention of stroke or TIA
Mechanism of Cilostazol: Elevation of cAMP

- Cilostazol
- Phospholipids
- Enzyme
- PGI2
- PGE1
- Adenylate Cyclase
- PDE III
- Ca²⁺
- Thromboxane Synthetase
- Cyclooxygenase
- Phospholipase A₂
- Phospholipid
- Arachidonic Acid
- ATP
- AMP
- cAMP
- Ca²⁺
- TXA₂
- ADP
- Serotonin
- GP IIb
- GP IIIa
- Degranulation
- Platelet
- Release Reaction

Decrease in carotid intima media thickness after 1 year of Cilostazol treatment in patients with type 2 diabetes mellitus

**[Methods]**
- Cilostazol Gr. (n=60) : Cilostazol 100 or 200mg/d during 1 year
  Placebo Gr. (n=60) : Placebo
- Measurement of CCA IMT using ultrasound after 6 and 12 months of treatment

**[Results]**

*** Changes of intima media thickness in common carotid arteries after 1 year of treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Cilostazol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg. IMT</td>
<td>0.02</td>
<td>-0.02</td>
</tr>
<tr>
<td>Max IMT</td>
<td>0.03</td>
<td>-0.01</td>
</tr>
<tr>
<td><strong>Right</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg. IMT</td>
<td>0.03</td>
<td>-0.02</td>
</tr>
<tr>
<td>Max IMT</td>
<td>0.09</td>
<td>-0.08</td>
</tr>
</tbody>
</table>

**[Conclusion]**

Cilostazol can be used effectively and safely for the control of atherosclerosis as assessed by IMT in diabetic patients.

*C.C. Ahn Diabetes Res Clin Pract, 2001*
Retrospective Evidence for CVD Prevention in T2DM pts

Brief report

Long-term effects of cilostazol on the prevention of macrovascular disease in patients with type 2 diabetes mellitus

Sang Youl Rhee\textsuperscript{a,b}, Young Seol Kim\textsuperscript{a,b,*}, Suk Chon\textsuperscript{a,b}, Seungjoon Oh\textsuperscript{a,b}, Jeong-taek Woo\textsuperscript{a,b}, Sung Woon Kim\textsuperscript{a,b}, Jin-Woo Kim\textsuperscript{a,b}

\textsuperscript{a} Department of Endocrinology and Metabolism, Kyung Hee University School of Medicine, Seoul, Republic of Korea
\textsuperscript{b} Research Institute of Endocrinology, Kyung Hee University, Seoul, Republic of Korea
Fig. 1 – Patient disposition of the current study.
## Total Macrovascular Disease Events in the Subjects


<table>
<thead>
<tr>
<th></th>
<th>Aspirin monotherapy (n = 401)</th>
<th>Aspirin combination (n = 187)</th>
<th>Cilostazol monotherapy (n = 296)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average follow-up period (years)</td>
<td>6.6 ± 2.3</td>
<td>7.5 ± 6.1</td>
<td>6.1 ± 2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total affected subjects (n, %)</td>
<td>44 (11.0)</td>
<td>24 (12.8)</td>
<td>31 (10.5)</td>
<td>0.711</td>
</tr>
<tr>
<td>Cardiovascular disease (n, %)</td>
<td>21 (5.2)</td>
<td>10 (5.3)</td>
<td>12 (4.1)</td>
<td>0.743</td>
</tr>
<tr>
<td>Cerebrovascular disease (n, %)</td>
<td>24 (6.0)</td>
<td>17 (9.1)</td>
<td>20 (6.8)</td>
<td>0.382</td>
</tr>
<tr>
<td>Peripheral arterial disease (n, %)</td>
<td>2 (0.5)</td>
<td>1 (0.5)</td>
<td>2 (0.7)</td>
<td>0.952</td>
</tr>
</tbody>
</table>
Total Macrovascular Disease Events in the Subjects

Fig. 2 – Survival analyses of the study subjects. By Gehan’s generalized Wilcoxon test, there were no significant differences of macrovascular disease free survival between each study subgroup.

Fig. 3 – By Cox proportional hazard model, there were also no significant differences of macrovascular disease free survival between each study subgroup.

The Phosphodiesterase Inhibitor Cilostazol Induces Regression of Carotid Atherosclerosis in Subjects With Type 2 Diabetes Mellitus

Principal Results of the Diabetic Atherosclerosis Prevention by Cilostazol (DAPC) Study: A Randomized Trial

Naoto Katakami, MD, PhD; Young-Seol Kim, MD, PhD; Ryuzo Kawamori, MD, PhD; Yoshimitsu Yamasaki, MD, PhD

Background—Antiplatelet drugs are effective in preventing recurrence of atherosclerosis in type 2 diabetic patients. However, the efficacy and usefulness of 2 different antiplatelet drugs, aspirin and cilostazol, in the progression of carotid intima-media thickening are unknown.

Methods and Results—To compare prevention by cilostazol and aspirin of progression of atherosclerosis, we conducted a prospective, randomized, open, blinded end point study in 4 East Asian countries. A total of 329 type 2 diabetic patients suspected of peripheral artery disease were allocated to either an aspirin-treated (81 to 100 mg/d) group or a cilostazol-treated (100 to 200 mg/d) group. The changes in intima-media thickness of the common carotid artery during a 2-year observation period were examined as the primary end point. The regression in maximum left, maximum right, mean left, and mean right common carotid artery intima-media thickness was significantly greater with cilostazol compared with aspirin (−0.088±0.260 versus 0.059±0.275 mm, \( P<0.001 \); −0.042±0.274 versus 0.045±0.216 mm, \( P=0.003 \); −0.043±0.182 versus 0.028±0.202 mm, \( P=0.004 \); and −0.024±0.182 versus 0.048±0.169 mm, \( P<0.001 \)). In a regression analysis adjusted for possible confounding factors such as lipid levels and hemoglobin A1c, the improvements in common carotid artery intima-media thickness with cilostazol treatment over aspirin treatment remained significant.

Conclusions—Compared with aspirin, cilostazol potently inhibited progression of carotid intima-media thickness, an established surrogate marker of cardiovascular events, in patients with type 2 diabetes mellitus.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: C000000215.

(Circulation. 2010;121:2584-2591.)

Key Words: aspirin ■ atherosclerosis ■ carotid arteries ■ diabetes mellitus ■ intima-media thickness
Patients with type 2 diabetes and arteriosclerosis obliterans from the Eastern Asian countries were registered online and randomly assigned either to the aspirin group (81–100 mg/day) or the cilostazol group (100–200 mg/day) in this international, 2-year, prospective follow-up interventional study.

Katakami N., Kim YS et al., Circulation 2010.
Study Disposition: DAPC study

Registered 329 patients

Aspirin Group 166 patients
- Excluded: 14 patients
  - Consent withdrawn: 2
  - Drop-out before treatment: 1
  - No baseline IMT: 11

Cilostazol Group 163 patients
- Excluded: 18 patients
  - Consent withdrawn: 5
  - Drop-out before treatment: 0
  - No baseline IMT: 13

Full analysis set 152 patients
- Study discontinued: 8 patients
  - Death: 2
    - Cerebral hemorrhage: 1
    - Suppurative cholangitis: 1
  - Non-fatal cardiovascular events: 2
    - Angina pectoris: 2
  - Adverse events: 4
    - Renal cell cancer: 1
    - Gastric cancer: 1
    - Hot flashes: 1
    - Rash/headache: 1
  - Drop-out: 10 patients
    - No visits: 6
    - Violation of drug use: 3
    - Others: 1

Full analysis set 145 patients
- Study discontinued: 9 patients
  - Death: 0
    - Non-fatal cardiovascular events: 4
      - Cerebral infarction: 2
      - TIA: 1
      - Angina pectoris: 1
  - Adverse events: 5
    - Treatment of thyroid cancer: 1
    - Gastrointestinal symptoms: 1
    - Dizziness: 1
    - Headache: 1
    - Shoulder pain/chest pain: 1
  - Drop-out: 20 patients
    - No visits: 15
    - No treatment with test drug: 2
    - Others: 3

Kakakami N., Kim YS et al., Circulation 2010.
Results (1): Change in max IMT

\[ \Delta \text{LCCA-max IMT} \]

Aspirin (n=152)
Cilostazol (n=145)

0.059
0.147mm
p<0.0001
-0.088

\[ \Delta \text{RCCA-max IMT} \]

Aspirin (n=152)
Cilostazol (n=145)

0.045
0.087mm
p=0.003
-0.042

Katakami N., Kim YS et al., Circulation 2010.
Results (2): Change in mean IMT

ΔLCCA-mean IMT

- Aspirin (n=152)
- Cilostazol (n=144)

ΔRCCA-mean IMT

- Aspirin (n=152)
- Cilostazol (n=144)

Katakami N., Kim YS et al., Circulation 2010.
Results (3): Changes of Lipid Profiles

Katakami N., Kim YS et al., Circulation 2010.
## Result (4): Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Cilostazol G</th>
<th>Aspirin G</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discontinuation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Suppurative cholangitis</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Cardiovascular events (non fatal)</strong></td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Adverse Events</strong></td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Dropout</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fails to visit the hospital</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Excluded concomitant medication</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Katakami N., Kim YS et al., Circulation 2010.
Cilostazol potently inhibited progression of carotid IMT, an established surrogate marker of cardiovascular events, in patients with T2DM suspected of having PAD compared with aspirin.

Katakami N., Kim YS et al., Circulation 2010.
Effect of cilostazol on carotid IMT in diabetic patients without cardiovascular event

Result

Changes IMT from baseline to 2 years. Data presented as mean(+SD)
*P values were calculated as interactions of treatment and time by linear mixed model adjusted for age, gender, DM duration, and statin use

### Table 2 Multivariable logistic regression models for mean carotid IMT progression at 2 years

<table>
<thead>
<tr>
<th></th>
<th>Adjusted OR</th>
<th>95% CI for OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM duration</td>
<td>1.084</td>
<td>1.016–1.156</td>
<td>0.015</td>
</tr>
<tr>
<td>Group I</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group II</td>
<td>0.825</td>
<td>0.278–2.449</td>
<td>0.729</td>
</tr>
<tr>
<td>Group III</td>
<td>0.121</td>
<td>0.037–0.383</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are adjusted for age, gender, BMI, current smoking, change of HbA1c from baseline to 2 years, change of LDL cholesterol from baseline to 2 years, change of systolic blood pressure from baseline to 2 years, statin use, baseline mean IMT.

*OR* odds ratio, *CI* confidence interval, *DM* diabetes mellitus
First prospective, multicenter, patient registration in Korean Subjects with type 2 Diabetes Mellitus

Consist of 12 University Hospitals
CAPPA (Cilostazol versus Aspirin for primary Prevention of Atherosclerotic Events)

Clinicaltrial.gov, NCT00886574
Cilostazol: Laboratory Evidences
Mechanism by which cilostazol treatment potently inhibited the progression of CIMT

due in part to improvement of lipid profiles

Cilostazol

![Diagram showing the mechanism of action of cilostazol on lipid profiles and enzyme activities.]

- cAMP ↑
- 5'AMP ↓
- LPL activity, LPL release ↑

- TG ↓
- HDL-C ↑
- Apo A/ Apo B ↑
- RLP ↓
- LPL activity ↑
- LPL release ↑
- RCT (Reverse cholesterol transport) ↑
Cilostazol inhibits vascular smooth muscle cell growth by downregulation of the transcription factor E2F

- Rat Carotid Artery

A. Control
B. Balloon Injured
C. Cilostazol 10 mg/kg
D. Cilostazol 30 mg/kg
E. Cilostazol 100 mg/kg

Cilostazol inhibited high glucose-induced VSMC proliferation.

* \( p < 0.01 \) vs control
# \( p < 0.05 \), ## \( p < 0.01 \) vs balloon injured.
Summary and Conclusions
Summary

- **Surrogate marker for sub-clinical atherosclerosis**
  - Clinical usefulness of IMT in T2DM subjects
  - IMT as a behavioral modifier?

- **Clinical Evidences of cilostazol**
  - Effective in IMT regression
  - Comparable outcome with aspirin for Korean T2DM subjects
  - Even in the primary prevention?
Summary

- Laboratory based evidences
  - Improvement of lipid profiles
  - Diminish neo-intimal formation in animal model
  - ROS↓
  - Cellular senescence↓ – possible age resister?
Conclusion

We can consider cilostazol as a useful treatment option for treatment and prevention of cardiovascular complications in Korean patients with T2DM