Effect of cilostazol on carotid intima media thickness in type 2 diabetic patients without cardiovascular event

Ji Hye Huh

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The Graduate School, Yonsei University
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Directed by Professor Bong Soo Cha

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Ji Hye Huh

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This certifies that the Master's Thesis of Ji Hye Huh is approved.

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Thesis Supervisor : Bong Soo Cha

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Thesis Committee Member#1: Byung-Wan Lee

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Thesis Committee Member#2: Sahng Wook Park

The Graduate School
Yonsei University

December 2013
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ABSTRACT

Effect of cilostazol on carotid intima media thickness in type 2 diabetic patients without cardiovascular event

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Department of Medicine
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(Directed by Professor Bong Soo Cha)

Objectives
We investigated the efficacy of cilostazol treatment for 2 years on the attenuation of carotid intima media thickness (IMT) progression in type 2 diabetic patients without cardiovascular disease history, as compared with other antiplatelet agents.

Methods
We recruited a total of 230 type 2 diabetic patients who had undergone IMT measurement twice within a 1.5–2.5 year (mean 2.06 ± 0.32 years) interval. Among these participants, we classified them into three groups according to antiplatelet agent administration at baseline: Group I (n = 66), antiplatelet naïve; Group II (n = 75), other antiplatelet agent administration; Group III (n = 50), cilostazol administration. We then analyzed the changes in clinical characteristics from baseline to 2 years.

Results
The changes in annual mean IMT at 2 years were 0.019 ± 0.045 mm/year, –0.001 ± 0.058 mm/year and –0.019 ± 0.043 mm/year for Group I, II and III, respectively (P < 0.001). Mean change in total cholesterol, low density lipoprotein (LDL)-cholesterol and triglyceride compared with baseline decreased the most in Group III even after adjustment for statin use. We also observed that the odds ratio of carotid IMT progression at 2
years was lowest in patients who were treated with cilostazol even after adjustment for change of metabolic parameters. When we categorized patients according to baseline carotid IMT tertile, the efficacy of cilostazol against carotid IMT progression was significant only when baseline IMT was over 0.662 mm (mean : 0.801).

**Conclusions**

Two-year treatment with cilostazol strongly inhibited carotid IMT progression compared to other antiplatelet agents in type 2 diabetic patients. This beneficial effect of cilostazol was significant when baseline IMT was thicker than 0.662 mm (mean 0.801 mm).

Key words : intima media thickness (imt), type 2 diabetes mellitus, cilostazol, lipid profiles
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I. INTRODUCTION

Diabetes mellitus is often associated with major cardiovascular diseases, such as coronary artery disease and stroke. In patients with type 2 diabetes mellitus (DM), the risk of coronary heart disease is 2- to 4-fold greater than that in the general population. Moreover, it has been suggested that diabetic patients without previous myocardial infarction have a risk equal to non-diabetic patients with previous myocardial infarction \(^1,2\). Therefore, it is widely believed that inhibiting the progression of atherosclerosis is important for preventing cardiovascular disease.

Currently, carotid artery intima-media thickness (IMT) is considered a useful surrogate marker for assessing the progression or regression of atherosclerosis in clinical trials \(^3,4\). Measurement of carotid IMT allows the noninvasive early detection of atherosclerotic changes. Indeed, a meta-analysis of eight studies involving 37,197 individuals has revealed that carotid IMT is a
strong predictor of future vascular events. For these reasons, it has been increasingly used as an endpoint in clinical trials. Actually, recent studies have investigated the efficacy of anti-diabetic medications, anti-hypertensive medications and statins on reduction of carotid IMT in type 2 diabetic patients. Antiplatelet agents are also broadly prescribed by many physicians for the primary prevention of cardiovascular disease. However, studies which investigated the effect of antiplatelet agents against carotid IMT progression have presented conflicting results. Because each antiplatelet agent has a different action mechanism on atherosclerosis, the resultant efficacy against IMT progression might differ. However, there are few studies assessing the effectiveness of different antiplatelet agents on IMT reduction, especially without history of overt cardiovascular disease.

Cilostazol, a phosphodiesterase III inhibitor, prevents inactivation of intracellular cAMP and leads to the inhibition of platelet aggregation and thrombus formation. Beyond its antiplatelet property, several studies have shown that cilostazol reduces inflammation, endothelial dysfunction, intimal hyperplasia, and smooth muscle cell proliferation, which underlie the favorable effects of cilostazol on atherosclerosis. Moreover, the results of several large-scale clinical trials have illustrated that that cilostazol can effectively prevent the progression of carotid atherosclerosis in patients with a history of cardiovascular disease. However, there are few studies analyzing the effectiveness of cilostazol on carotid IMT regression in subjects without history of overt
cardiovascular disease.

On the basis of these findings, we hypothesized that cilostazol might have a stronger effect in carotid IMT reduction than other antiplatelet agents, and aimed to confirm its efficacy on the inhibition of carotid IMT progression through comparison with other antiplatelet agents in diabetic patients without cardiovascular disease history. In addition, we also investigated the predictive baseline carotid IMT that corresponds to cilostazol efficacy.
II. MATERIALS AND METHODS

1. Study population and design

In this clinical, retrospective longitudinal study, we reviewed 230 patients who were enrolled in the diabetes registry of the Severance Diabetes Center between June 2005 and June 2013. We recruited adult participants who had undergone carotid IMT measurement twice over a 1.5–2.5 year interval (mean 2.06 ± 0.32 years) and measured metabolic parameters including glucose and lipid profile at baseline, 1 and 2 years. Exclusion criteria included a history of cardiovascular disease, cerebral vascular disease, or peripheral artery disease as assessed thorough examinations before enrollment, severe liver or kidney disease (Cr>1.7), thyroid disorders, type I diabetes, malignant disease, fibrate user and two or more antiplatelet agent user. We also excluded patients who were changed medication such as statin, anti-diabetic agent and antiplatelet agent by physician during follow up period. The study protocol was approved by the Ethics Committee of Yonsei University College of Medicine. Type 2 diabetes was diagnosed based on the current criteria of the American Diabetes Association 15.

2. Assessments

Among 230 patients with type 2 diabetes, we excluded a coumadin user (n = 3) and those who had a history of using antiplatelet agents for more than three months before baseline (n = 35). According to antiplatelet administration at baseline, we classified the remaining individuals into the following three groups:
Group I (n = 66), antiplatelet naïve; Group II (n = 75), other antiplatelet agent administration; Group III (n = 50), cilostazol administration (Fig. 1). The following parameters were recorded and analyzed: changes in glucose parameters, changes in lipid profiles and changes in urine albumin excretion at baseline, 1 and 2 years. Blood samples were collected from participants after an overnight fast. Plasma glucose was measured using the glucose oxidase method. Plasma triglycerides (TG), total cholesterol, and high-density lipoprotein (HDL) cholesterol were assayed using a routine Hitachi 7600 autoanalyzer (Hitachi Instruments Service, Tokyo, Japan). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation.
Figure 1. Subject profiles
3. Measurement of carotid intima media thickness

The annual change in mean IMT (mm/yr) \[ \Delta \text{IMT} = (\text{follow-up mean IMT} - \text{baseline mean IMT})/\text{follow-up period} \] during the study period was calculated. IMT measurement has been described in detail in previous reports \(^{16}\). Briefly, common carotid arterial ultrasound examinations were conducted by two specialized technicians using an Aloka ProSound ALPHA 10 (HITACHI, Tokyo, Japan) with a 13 MHz linear probe. We performed B mode examinations 1.5 cm proximal to the carotid bifurcation on the far wall of the common carotid artery and on both sides. IMT was defined as the distance between the media-adventitia interface and the lumen-intima interface. Both carotid arteries were divided into total carotid region, carotid opening, and carotid branch, and the maximum measurement in each region was obtained to define the maximum IMT. Mean IMT was considered as the average of right and left mean IMT, which is the mean value of computer-based points in the region \(^{17}\). Reproducibility was further tested for carotid IMT measurements: inter-observer coefficient of variation (CV) was 2.11%, and the day-to-day coefficient of variation was 2.06% Plaques were defined according to the Mannheim consensus \(^{18}\), by which a plaque is diagnosed when the vessel wall thickness is greater than 1.5 mm or when the vessel wall appears to be at least 0.5 mm or 50% thicker than the surrounding wall.

4. Statistical analysis

All statistical analyses were performed with PASW statistical software (version
One-way analysis of variance (ANOVA) test was used to compare differences in clinical characteristics among the groups. For categorical variables, a chi-square test was used to compare frequencies among the groups. To assess differences in carotid IMT between the three groups at baseline and 2 years, as well as lipid profiles at baseline, 1 and 2 years, we performed a linear mixed model for repeated measurements. Two effects were included: one between-groups antiplatelet agent treatment effect [based on Group I, II, III] and one within-group time effect (time: years 1, and 2). Analyses in the mixed model were adjusted for age, sex, DM duration, and statin use. The changes in outcomes from baseline to 1 and 2 years were assessed using paired t-test. Multiple logistic regression analysis was used to examine the association between antiplatelet agent use and IMT progression after adjusting for change of metabolic parameters.
III. RESULTS

1. General and biochemical characteristics

Table 1 summarizes the baseline characteristics of the participants by group. Except for one participant, no one suffered symptomatic cardiovascular events, such as stroke or coronary artery disease, during the follow-up period. One person suffered a coronary artery occlusive event, 6 months after the administration of saprogrelate. We excluded him from the analyses because he had used dual antiplatelet agents after the cardiovascular event. Current smoker was high in Group II. Baseline mean IMT, maximum IMT, and the proportion of initial plaque presence at carotid artery were higher in Group III than in other groups. In addition, total cholesterol and LDL cholesterol at baseline were also higher in Group III. Other clinical characteristics including age, sex, DM duration, anti-diabetic agent use except thiazolidinedione, angiotensin receptor blocker and angiotensin converting enzyme (ACE) inhibitor use, statin use, HDL cholesterol, TG, glucose parameter and urine albumin excretion were similar between the three groups.
Table 1. Baseline characteristics of study subjects according to antiplatelet agent use

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 66)</td>
<td>(n = 75)</td>
<td>(n = 50)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58.43 ± 8.14</td>
<td>60.66 ± 8.32</td>
<td>60.46 ± 7.56</td>
<td>0.217</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>26 (39.4%)</td>
<td>35 (46.7%)</td>
<td>27 (54%)</td>
<td>0.292</td>
</tr>
<tr>
<td>DM duration (yr)</td>
<td>11.05 ± 6.11</td>
<td>11.55 ± 7.325</td>
<td>10.18 ± 7.3</td>
<td>0.558</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>0 (0%)</td>
<td>7 (4.2%)</td>
<td>4 (2.4%)</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.54 ± 2.93</td>
<td>24.06 ± 3.95</td>
<td>25.41 ± 33.74</td>
<td>0.029</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.91 ± 0.05</td>
<td>0.91 ± 0.05</td>
<td>0.92 ± 0.05</td>
<td>0.285</td>
</tr>
<tr>
<td>Baseline mean IMT (mm)</td>
<td>0.64 ± 0.109</td>
<td>0.767 ± 0.13</td>
<td>0.776 ± 0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline maximum IMT (mm)</td>
<td>0.756 ± 0.13</td>
<td>0.926 ± 0.177</td>
<td>0.929 ± 0.194</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plaque presence, n (%)</td>
<td>29 (43.9%)</td>
<td>53 (70.7%)</td>
<td>38 (76%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Anti-diabetic medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinedione, n (%)</td>
<td>39 (59.1%)</td>
<td>36 (48%)</td>
<td>14 (28%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Metformin, n (%)</td>
<td>56 (84.8%)</td>
<td>66 (88%)</td>
<td>43 (86%)</td>
<td>0.858</td>
</tr>
<tr>
<td>Sulfonylurea, n (%)</td>
<td>36 (54.5%)</td>
<td>42 (56%)</td>
<td>30 (60%)</td>
<td>0.836</td>
</tr>
<tr>
<td>α-glucosidase inhibitor</td>
<td>8 (8.2%)</td>
<td>4 (8.2%)</td>
<td>2 (5.6%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Insulin, n (%)</td>
<td>9 (13.6%)</td>
<td>9 (12%)</td>
<td>6 (12%)</td>
<td>0.949</td>
</tr>
<tr>
<td>ACE inhibitor, ARB, n (%)</td>
<td>42 (63.6%)</td>
<td>46 (61.3%)</td>
<td>26 (52%)</td>
<td>0.419</td>
</tr>
<tr>
<td>Statin use, n (%)</td>
<td>25 (37.9%)</td>
<td>33 (44%)</td>
<td>25 (50%)</td>
<td>0.424</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.88 ± 0.18</td>
<td>0.90 ± 0.18</td>
<td>0.92 ± 0.17</td>
<td>0.466</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>135.97 ± 14.23</td>
<td>135.26 ± 16.08</td>
<td>135.33 ± 14.46</td>
<td>0.956</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.15 ± 5.63</td>
<td>77.74 ± 7.34</td>
<td>79.39 ± 5.68</td>
<td>0.279</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>171.11 ± 31.18</td>
<td>178.36 ± 37.65</td>
<td>187.96 ± 35.16</td>
<td>0.038</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>49.32 ± 9.57</td>
<td>49.23 ± 11.72</td>
<td>48.84 ± 9.51</td>
<td>0.968</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>93.51 ± 28.76</td>
<td>101.28 ± 36.48</td>
<td>111.72 ± 31.54</td>
<td>0.013</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>145.77 ± 86.57</td>
<td>142.28 ± 67.44</td>
<td>151.04 ± 72.52</td>
<td>0.822</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>131.35 ± 40.67</td>
<td>139.98 ± 43.1</td>
<td>141.46 ± 45.65</td>
<td>0.368</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.47 ± 1.44</td>
<td>7.72 ± 1.55</td>
<td>7.81 ± 1.45</td>
<td>0.424</td>
</tr>
<tr>
<td>Urine albumin excretion</td>
<td>28.39 ± 64.71</td>
<td>43.87 ± 148.46</td>
<td>37.11 ± 52.60</td>
<td>0.695</td>
</tr>
</tbody>
</table>
Data presented as n (%) or mean ± standard deviation. BMI, body mass index; IMT, intima media thickness; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; FPG, fasting plasma glucose.
2. Effect of antiplatelet agent on carotid IMT change and plaque

Figure 2 shows changes in mean and maximum IMT from baseline to 2 years. Both mean and maximum IMT showed most pronounced reduction in Group III and it was still significant after adjustment for age, sex, DM duration, statin use (P < 0.001). Annual change from baseline to 2 years for mean carotid IMT was 0.019 ± 0.045 mm/yr for Group I, –0.001 ± 0.058 mm/yr for Group III, and −0.019 ± 0.043 mm/yr for Group III (P < 0.001) (Supplemental Table 1). Annual change from baseline to 2 years for maximum carotid IMT also most declined in Group III (0.027 ± 0.068 mm/yr for Group I, –0.005 ± 0.093 mm/yr for Group II, and −0.001 ± 0.059 mm/yr for Group III) (P < 0.001) (Supplemental Table 1). However, treatment with all types of antiplatelet agents did not result in change in plaque number (P = 0.224) (Supplemental Table 1). Change in HbA1c and urine albumin excretion from baseline to 2 years was not significantly different among the three groups (Supplemental Table 1).
Figure 2. Changes in **a** mean and **b** maximum intima-media thickness (IMT) from baseline to 2 years. Data presented as mean (±standard deviation).
*P values were calculated as interactions of treatment and time by linear mixed model adjusted for age, gender, DM duration, and statin use.
3. Serum lipid change

Figure 3 and Supplemental Table 1 show changes in serum lipids from baseline to 1 and 2 years. Among the three groups, total cholesterol and LDL cholesterol at 1 and 2 years were reduced the most in Group III. On the other hand, TG was significantly reduced by $-30.49 \pm 78.49$ at 2 years only in Group III (Supplemental Table 1). Using a linear mixed model after adjustment for age, sex, DM duration and statin use, the most prominent decrements in total cholesterol and LDL cholesterol at 1 and 2 years in Group III remained significant ($P < 0.001$) (Fig. 3a and 3b). However, statistically significant decrements in TG at 1 and 2 years in Group III were not observed in linear mixed model analysis ($P = 0.621$). HDL cholesterol, HbA1c and urine albumin excretion were not statistically changed at 1 and 2 years in all groups and no between-group difference in changes for these parameters at 1 and 2 years were observed.
Figure 3. Changes of lipid profiles from baseline to 1 and 2 years in three groups.  

a total cholesterol. b low density lipoprotein (LDL) cholesterol.

*P values were calculated as interactions of treatment and time by linear mixed model adjusted for age, gender, DM duration, and statin use.
Supplemental table 1. Changes in IMT and metabolic parameters from baseline to 1 and 2 years

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n=66)</th>
<th>Group II (n=75)</th>
<th>Group III (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IMT change (mm/yr)</td>
<td>0.019±0.045*</td>
<td>-0.001±0.058</td>
<td>-0.019±0.043*†</td>
</tr>
<tr>
<td>Maximum IMT change (mm/yr)</td>
<td>0.027±0.068*</td>
<td>-0.005±0.093</td>
<td>-0.001±0.059*†</td>
</tr>
<tr>
<td>Plaque regression at 2 year, n (%)</td>
<td>0(0%)</td>
<td>2(2.7%)</td>
<td>3(6.0%)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change at 1 year</td>
<td>-1.56±33.03</td>
<td>-5.94±40.49</td>
<td>-21.46±41.26*†</td>
</tr>
<tr>
<td>Mean change at 2 year</td>
<td>2.55±42.13</td>
<td>-12.29±46.19</td>
<td>-17.43±42.18*†</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change at 1 year</td>
<td>0.42±29.07</td>
<td>-5.84±37.69</td>
<td>-23.09±34.39*†</td>
</tr>
<tr>
<td>Mean change at 2 year</td>
<td>5.32±37.22</td>
<td>-11.01±41.71*</td>
<td>-18.48±37.37*†</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change at 1 year</td>
<td>-11.44±84.27</td>
<td>-1.17±66.43</td>
<td>-12.72±90.36</td>
</tr>
<tr>
<td>Mean change at 2 year</td>
<td>-14.73±76.52</td>
<td>-20.74±70.81</td>
<td>-30.49±78.49*</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change at 1 year</td>
<td>-0.56±7.92</td>
<td>-0.49±7.61</td>
<td>1.19±7.53</td>
</tr>
<tr>
<td>Mean change at 2 year</td>
<td>-0.70±7.35</td>
<td>-0.44±9.38</td>
<td>1.90±10.44</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change at 2 year</td>
<td>-0.06±1.26</td>
<td>-3.34±24.16*</td>
<td>-0.3±1.51</td>
</tr>
<tr>
<td>Urine albumin excretion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change at 2 year</td>
<td>15.66±99.72</td>
<td>44.25±306.58</td>
<td>34.73±207.03</td>
</tr>
</tbody>
</table>

Data presented as n (%) or mean ± standard deviation.
* P <0.05, compared with baseline by paired t-test.
† P <0.05, compared with group 1 and 2 by one-way ANOVA.
4. The association between cilostazol treatment and inhibition of carotid IMT progression

We performed a multivariable logistic regression analysis to determine the effect of antiplatelet agents on inhibition of carotid IMT progression after adjusting for confounding factors such as age, gender, DM duration, body mass index (BMI), current smoking, changes in HbA1c at 2 year, changes in LDL cholesterol at 2 year, changes in systolic blood pressure at 2 year, statin use and baseline mean IMT. As shown in Table 2, even after adjustment for confounding factors, there was still strong association between cilostazol treatment for 2 years and inhibition of IMT progression (OR = 0.825, 95% CI = 0.278–2.449 in Group II; OR = 0.121, 95% CI = 0.037–0.383 in Group III). DM duration also increased the odds ratio for IMT progression at 2 year (OR = 1.084, 95% CI = 1.016–1.156). Considering there were slight differences in baseline carotid IMT among the groups and to determine the appropriate baseline IMT that necessitates treatment by an antiplatelet agent, the effect of antiplatelet agents against carotid IMT progression was also examined by baseline carotid IMT category. When we categorized baseline carotid IMT into tertiles (first <0.662 mm; second = 0.662–0.78 mm; third>0.78 mm), we observed that the beneficial effect of cilostazol against carotid IMT progression was significant in the second and third tertiles of baseline carotid IMT (thicker than a mean of 0.801 mm; range ≥ 0.662) (Table 3).
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 year, change of LDL cholesterol from baseline to 2 year, change of systolic blood pressure from baseline to 2 year, statin use, baseline mean IMT OR, odds ratio; CI, confidence interval; DM, Diabetes mellitus
Table 3. Mean annual changes from baseline in carotid intima media thickness (IMT) according to baseline carotid IMT tertile subgroups

(A) 1st tertile, (B) 2nd and 3rd tertile.

<table>
<thead>
<tr>
<th>Baseline IMT&lt;0.662 (mean : 0.591 ± 0.071)</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 40)</td>
<td>(n = 13)</td>
<td>(n = 11)</td>
<td></td>
</tr>
<tr>
<td>Mean IMT (mm/yr)</td>
<td>0.022 ± 0.053</td>
<td>0.01 ± 0.05</td>
<td>-0.003 ± 0.027</td>
<td>0.324</td>
</tr>
<tr>
<td>Maximum IMT (mm/yr)</td>
<td>0.033 ± 0.081</td>
<td>0.007 ± 0.047</td>
<td>-0.003 ± 0.034</td>
<td>0.234</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline IMT≥0.662 (mean : 0.801 ± 0.108)</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 26)</td>
<td>(n = 63)</td>
<td>(n = 39)</td>
<td></td>
</tr>
<tr>
<td>Mean IMT (mm/yr)</td>
<td>0.015 ± 0.027</td>
<td>-0.004 ± 0.060</td>
<td>-0.023 ± 0.046</td>
<td>0.014</td>
</tr>
<tr>
<td>Maximum IMT (mm/yr)</td>
<td>0.018 ± 0.04</td>
<td>-0.007 ± 0.1</td>
<td>-0.033 ± 0.064</td>
<td>0.044</td>
</tr>
</tbody>
</table>
IV. DISCUSSION

In this retrospective longitudinal study we found a significant regression of carotid IMT among type 2 diabetic patients treated with cilostazol for 2 years. Subjects who were treated with cilostazol for 2 years showed significant decrease in total cholesterol, LDL-cholesterol, TG. Finally, we also demonstrated that the effect of cilostazol was more pronounced in patients treated with cilostazol in cases where the baseline carotid IMT was on average thicker than 0.801 mm. These discoveries also suggest that cilostazol might prevent atherosclerosis progression in type 2 diabetic patients who are at the moderate risk for cardiovascular events, probably in part through improvement of lipid profiles.

Diabetes mellitus is one of the major risk factors for atherosclerosis because hyperglycemia is associated with an inflammatory disease of the arterial wall, in which leukocytes and oxidized lipoproteins accumulate, leading to formation of fatty stripes and atherosclerotic plaques. Therefore, therapeutic strategy targeting these subsequent cascades is important for type 2 diabetic subjects to prevent the progression of atherosclerosis. Among these therapeutic strategies, most clinical practice guidelines recommend aspirin as the first line medication for the prevention of macrovascular complications in patients with type 2 diabetes at present. Nevertheless, recent studies have demonstrated that cilostazol therapy is associated with significant improvement in carotid atherosclerosis in comparison with aspirin. These studies, however, included secondary prevention patients, who are generally at the highest risk for
cardiovascular events. Because there is a paucity of systemic data on the efficacy of cilostazol on atherosclerosis in type 2 diabetic patients without history of cardiovascular event, we investigated the efficacy of cilostazol on IMT in them through comparison with other antiplatelet agents.

In our study, we observed a prominent inhibitory effect against IMT progression in patients who were treated with cilostazol compared to other groups. This result indicates that cilostazol might have a stronger potency for preventing the progression of atherosclerosis than other agents. The reasons for the effective attenuation of atherosclerosis progression could be explained by the following action mechanisms of cilostazol: First possible action mechanism is improvement in lipid profile by cilostazol. Rizzo et al reported that cilostazol can significantly lower plasma triglyceride levels, as well as improve other pro-atherogenic lipid profiles, including remnant-like particles, apolipoprotein B and postprandial lipemia. Additionally, Ueno et al. demonstrated that cilostazol has been shown to significantly decrease small dense LDL cholesterol in type 2 diabetic patients. Like previous studies, our study also demonstrated improvement of lipid profiles in patients treated with cilostazol. Second, cilostazol is a different type of antiplatelet agent that inhibits type 3 phosphodiesterase and decreases thromboxane formation by enhancement of the platelet/cAMP level. The increase in cAMP level leads to an inhibition of platelet aggregation, vasodilation, and vascular smooth muscle cell proliferation, an increase in heart rate and contractile force, and an improved lipid metabolism. Finally, previous studies have
demonstrated that cilostazol was associated with significant decrease in high sensitive C-reactive protein, total leukocyte count. Moreover, Wada et al. reported that cilostazol suppressed TNFα production from macrophages and attenuated TNFα-induced chronic inflammation in adipose tissue, leading to the improvement of glucose intolerance and insulin resistance in obese diabetic mice. It indicates that cilostazol has anti-inflammatory effects, which may play an important role in inhibiting the progression of atherosclerosis. Taken together, we can speculate that cilostazol might have pleiotropic effects on inhibiting atherosclerosis aside from its effects on the platelet and these action mechanisms may lead a strong regression of atherosclerosis.

The major findings of this study include the demonstration of improvement of lipid profiles as well as a strong efficacy against atherosclerosis in patients treated with cilostazol. Our study demonstrated a prominent decline of total cholesterol, LDL cholesterol and TG in patients treated with cilostazol. This improvement in lipid profiles, especially total cholesterol and LDL-cholesterol, by cilostazol was independent of statin use. However, in our study, HDL-cholesterol was not changed in the cilostazol treatment group. Though many other studies have suggested probable mechanisms on improvement in lipid profile by cilostazol, the exact metabolic mechanism of cilostazol remains to be definitively proved. Furthermore, we cannot assume that the anti-atherosclerotic effect of cilostazol is dependent solely on improvement in pro-atherogenic lipid profile because, even after adjusting for change in HbA1c, lipid profile and administration of statin, the
beneficial effects of cilostazol were still significant in our study.

At present, there is no consensus for the baseline IMT that necessitates treatment by antiplatelet agents, especially in diabetic patients without cardiovascular events. Therefore, we also investigated the efficacy of cilostazol according to baseline IMT. As a result, the beneficial effect of cilostazol against carotid IMT progression was significant when baseline IMT was thicker than a mean of 0.801 mm (Table 3). From these findings, we can speculate that it is reasonable to administrate cilostazol for patients at moderate risk in IMT.

This study has several limitations. First, because of the single center and retrospective nature of the study, the impacts of the results may be weakened. Furthermore, a causal relationship between anti-atherosclerotic effect of cilostazol and improving pro-atherogenic lipid profile could not be definitely established. Second, because of the inclusion criteria and classification, the number of eligible participants in each group was small. Third, although we controlled for statin use as well as change of metabolic parameters, because this was not a randomized and controlled study, other factors may have influenced the results. Finally, we also did not measure change of inflammatory marker such as IL-6, TNFα which can explain mechanism of efficacy on atherosclerosis of cilostazol.

In conclusion, our study is the first study to examine the efficacy of cilostazol against carotid IMT progression in type 2 diabetic subjects without history of cardiovascular disease. We found that cilostazol is more beneficial to the regression of carotid IMT than other antiplatelet agents. Moreover, cilostazol
might contribute to improvement in lipid profiles and reduction of atherosclerotic proliferation independent of statin use. This study also suggests that when baseline carotid IMT is over at least 0.801 mm treatment with cilostazol may be helpful to controlling carotid atherosclerosis in type 2 diabetic patients regardless of history of cardiovascular events. Further studies are needed to establish whether cilostazol treatment may be considered a new therapeutic approach to modulate atherogenic dyslipidemia.
V. CONCLUSION

Two-year treatment with cilostazol strongly inhibited carotid IMT progression compared to other antiplatelet agents in type 2 diabetic patients. This beneficial effect of cilostazol was significant when baseline IMT was thicker than 0.662 mm (mean 0.801 mm).
REFERENCES


19. Hansson GK. Inflammation, atherosclerosis, and coronary artery


심혈관 질환의 과거력이 없는 2형 당뇨병 환자에서 cilostazol이 경동맥 두께에 미치는 효과의 분석

<지도교수 차봉수>
연세대학교 대학원 의학과

허지혜

최근, 2형 당뇨 환자에서, 경동맥 두께를 줄이기 위한 항혈소판제제의 처방이 늘어나고 있다. 항혈소판제제 중 Cilostazol은 고지혈증의 호전, 염증 반응의 감소, 혈관평활근의 감소 등의 다양한 기전으로, 동맥경화증의 진행을 늦추는 데 있어 다른 혈소판제제보다 강력한 효과가 있을 것으로 기대된다. 그러나, 현재 항혈소판제제들의 경동맥 두께에 미치는 영향을 비교 분석한 연구는 거의 없으며, 특히 심혈관질환의 과거력이 없는 고위험군을 대상으로 한 연구는 희박하다. 따라서, 이번 연구에서는 심혈관질환이 없었던 2형 당뇨환자에서 항혈소판제제들이 경동맥 두께에 미치는 영향을 비교 분석하였다. 세브란스병원 내원환자 중 2년 간격으로 두 번 이상 경동맥 두께를 측정한 당뇨환자 230명을 대상으로, 기준 시점에서 어떠한 항혈소판제제를 첨가하였는지에 따라 총 세 군으로 나누었다; 1군은 항혈소판제제를 첨가하지 않은 군으로, 66명이었고, 2군은 Cilostazol 이외에 다른 항혈소판제제를 첨가한 75명이었으며, 3군은 Cilostazol을 첨가한 50명이었다. 총 2년간 후향적으로, 추적관찰한 결과, 2군 계, 평균 경동맥 두께의 연간 변화율은 1군에서 0.019 ± 0.045 mm/년, 2군에서 -0.001 ± 0.058 mm/년 그리고 3군에서 -0.019 ± 0.043 mm/년 (P < 0.001) 였다. 치료 2년째, 총 콜레스테롤과 저밀도콜레스테롤, 그리고 중성지방의
감소는 3군에서 가장 뒤졌으며, 이는 고지혈증 약제 사용을 보정함에도 불구하고 유의하였다. 하지만, 추적 관찰한 2년 동안의 콜레스테롤 변화를 비롯한 다른 대사적인 측면의 변화를 보정한 상태에서도, Cilostazol 이 경동맥 두께의 증가를 막는 강력한 효과는 유의하게 나타났다. 그리고, Cilostazol 의 이러한 효과는 기준 시점의 경동맥 두께가 평균 0.801mm 이상일 때 유의한 것으로 나타났다. 결론적으로, 본 연구에서는 2년간의 Cilostazol 치료는 경동맥 두께의 감소에 있어 다른 항 혈소판제제보다 강력한 효과를 나타낸을 확인하였다. 이러한 효과에는 부분적으로, Cilostazol 사용으로 인한 고지혈증의 개선이 원인이 될 수 있을 것이고, 그 외에 동맥경화의 과정을 차단하는 다른 다양한 효과들도 영향을 미쳤을 것으로 생각된다.