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# Effect of cilostazol on arterial stiffness and vascular adhesion molecules in type 2 diabetic patients with metabolic syndrome: a randomised, double-blind, placebo-controlled, crossover trial

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## Abstract

**Background:** The phosphodiesterase inhibitor cilostazol has beneficial effects on atherosclerosis by virtue of vasodilatory and antiplatelet effects. However, less is known about the effect of cilostazol on arterial stiffness and biochemical markers related to vascular inflammation and endothelial dysfunction in type 2 diabetic patients with metabolic syndrome.

**Methods:** In this randomized, double-blind, crossover trial, 45 diabetic patients with metabolic syndrome were randomly assigned to either the cilostazol group (50 mg for 2 weeks, 100 mg for 6 weeks) or placebo group for an 8-week treatment phase, and then crossed over. Brachial-ankle pulse wave velocity (baPWV) and serum levels of inflammatory cytokines and vascular cellular adhesion molecules were measured before and after each treatment phase.

**Results:** Compared with the placebo group, the mean baPWV did not improve in the cilostazol group (mean difference 31.42 cm/sec, 95% CI -55.67 to 118.5). Cilostazol treatment significantly reduced soluble vascular cellular adhesion molecule-1 (sVCAM-1) level (from 1288.7 ± 285.6 to 1168.2 ± 252.3 ng/dL,  $P = 0.0003$ ), and there was also significant mean difference between groups (mean difference 105.18 ng/dL, 95% CI 10.65 to 199.71). However, other biochemical markers including lipid profiles, high sensitivity C-reactive protein, adiponectin, interleukin-6, tumor necrosis factor-alpha, monocyte chemoattractant protein-1, and soluble intercellular adhesion molecule-1 did not improve with cilostazol treatment.

**Conclusion:** Cilostazol treatment significantly reduced serum sVCAM-1 level, but this short term treatment was not associated with beneficial effect on arterial stiffness and other inflammatory markers.

**Trial registration:** (Clinical trial reg. no. NCT00573950, clinicaltrials.gov.)

**Keywords:** Cilostazol, Phosphodiesterase inhibitor, Arterial stiffness, Vascular adhesion molecules, Type 2 diabetes, Metabolic syndrome

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## Introduction

Cardiovascular disease (CVD) is the major cause of mortality in patients with diabetes and metabolic syndrome. Chronic inflammation and endothelial dysfunction appear to be major components contributing to the development of atherosclerosis in a background of insulin resistance in diabetic patients [1,2]. Biochemical markers such as proinflammatory cytokines and vascular cellular adhesion molecules are related to the progression of atherosclerosis and CVD [3,4] and are also helpful for the screening of subclinical atherosclerosis [5,6].

On the other hands, subclinical atherosclerosis and increased arterial stiffness are early changes predicting the development of CVD. Various noninvasive measures of these changes, such as carotid intima-media thickness (IMT), pulse wave velocity (PWV), and coronary artery calcification have been developed and commonly used [7]. Of these methods, PWV is the most commonly used measure of arterial stiffness, and predicts the development of CVD and mortality in type 2 diabetes [8].

Cilostazol is a selective inhibitor of cyclic phosphodiesterase 3, which is used for the treatment of chronic peripheral artery disease, by virtue of its antiplatelet and vasodilatory activities [9]. A growing body of evidence obtained from animal models suggests that cilostazol has beneficial effects on lipid metabolism either by cAMP-mediated increases in lipoprotein lipase, or by inhibiting the production of cytokines related to the progression of atherosclerotic lesions [10,11].

Previous clinical studies showed that cilostazol treatment attenuated the progression of carotid IMT in type 2 diabetic patients [12,13]. The favorable effects of cilostazol on atherosclerosis were also demonstrable in diabetic patients with known peripheral artery disease (PAD); soluble CD40 ligand and hs-CRP levels were significantly decreased, and arterial compliance was modestly improved [14,15]. However, the effects on arterial stiffness and various inflammatory markers related to the progression of atherosclerosis have not been evaluated in subjects with type 2 diabetes but not having coronary heart disease or PAD. Therefore, we conducted a randomized, double-blind, crossover study to clarify the efficacy of cilostazol in preventing the progression of arterial stiffness using brachial-ankle PWV (baPWV) in patients with type 2 diabetes and metabolic syndrome. We also evaluated the effect of cilostazol on proinflammatory cytokines and inflammatory markers related to vascular inflammation and endothelial dysfunction.

## Materials and methods

### Subjects and study design

The eligible participants were patients aged over 18 years with type 2 diabetes and metabolic syndrome.

Type 2 diabetes was defined by the American Diabetes Association criteria [16]. All patients had been treated with oral hypoglycemic agents or insulin. Metabolic syndrome was defined according to Adult Treatment Panel III of the National Cholesterol Education Program guidelines [17], modified in accordance with the World Health Organization's proposed waist circumference (WC) cut-off points for Asians. Subjects with metabolic syndrome were required to meet three or more of the following criteria: WC  $\geq 90$  cm in men and  $\geq 80$  cm in women, serum triglyceride level  $\geq 150$  mg/dL, HDL-cholesterol (HDL-C) levels  $< 40$  mg/dL in men and  $< 50$  mg/dL in women, impaired fasting glucose  $\geq 100$  mg/dL or anti-diabetic treatment, and blood pressure  $\geq 130/85$  mmHg or treatment for hypertension.

Subjects who had taken a stable dose of anti-hypertensive or lipid-lowering drugs for at least 8 weeks before the study were enrolled, and these medication dosages were maintained throughout the study. The major exclusion criteria included known CVDs including coronary heart disease and peripheral artery disease; congestive heart failure; severe hepatic dysfunction and renal dysfunction; treatment with thiazolidinone within 8 weeks at screening; current use of anticoagulants, antiplatelet agents, and corticosteroid supplements; and history of drug or alcohol abuse. All subjects gave informed consent and the protocol was approved by the Institutional Review Board of Korea University Hospital.

Of 49 Korean subjects screened, 4 did not meet the diagnostic criteria of metabolic syndrome. As a result, 45 Korean patients were randomly assigned to receive cilostazol (50 mg for the first 2 weeks and 100 mg for the next 6 weeks) or matching placebo for 8 weeks. The dose titration was set to minimize adverse events related to study medications.

With a washout period of 8 weeks, participants were then crossed over to the other treatment arm for a further 8 weeks. Cilostazol and placebo tablets were supplied by Otsuka Pharmaceuticals (Tokyo, Japan). The tablets were identical in size, color, and taste. All participants underwent a comprehensive physical examination, anthropometric measurements, and blood sampling for biochemical analyses, and baPWV measurements at baseline and after treatment at each treatment phase. Blood pressure was measured in a standardized manner with a mercury sphyngomanometer; two separate measurements were taken after 5 min of rest and the mean was calculated. Anthropometric measurements were taken after an overnight fast. Height, body weight, BMI ( $\text{kg}/\text{m}^2$ ), and WC of all subjects were recorded. Blood was drawn for biochemical analysis after an overnight fast. This clinical trial is registered as NCT00573950 at [clinicaltrials.gov](http://clinicaltrials.gov).

### Measurement of arterial stiffness

Arterial stiffness was assessed by baPWV, which was measured using a model BP-203RPE II volume-plethymographic apparatus (Colin, Komaki, Japan). Each participant was examined in a supine position with electrocardiographic electrodes placed on both wrists and cuffs wrapped around both brachia and ankles. The pulse waveforms were recorded using a semiconductor pressure sensor. Transmission time was calculated as the time for the waveform to travel between the right arm and both ankles, and the transmission distance between the right brachium and ankle was automatically calculated based on the height of the participant. The baPWV was automatically calculated by dividing transmission distance by the transmission time. The means of right and left baPWV were used for the analysis.

### Measurement of biochemical markers

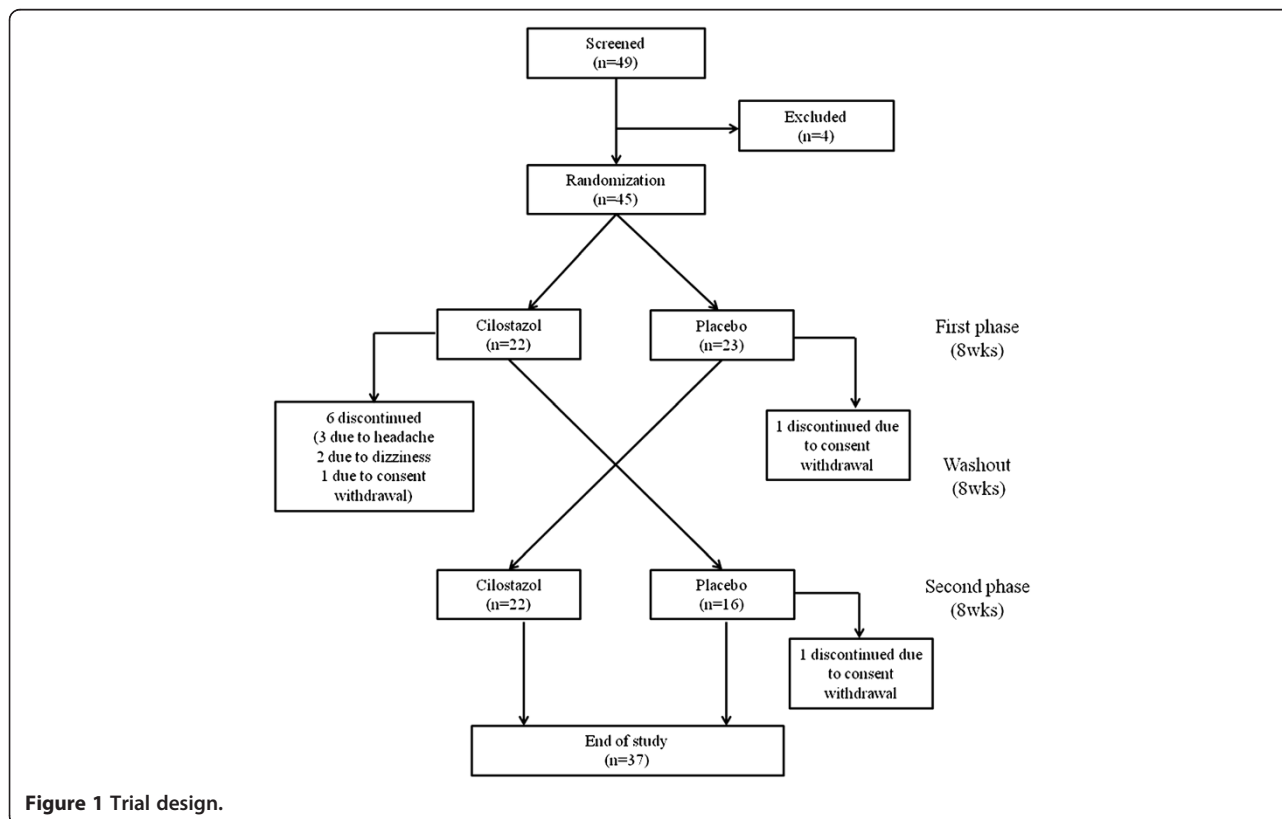
Venous blood samples were drawn from each patient after overnight fasting. Blood samples were centrifuged to obtain serum, and the serum was stored at  $-80^{\circ}\text{C}$ . High sensitivity C-reactive protein (hsCRP) levels were measured using a CRP ELISA kit (Immunodiagno, Bensheim, Germany); the intra- and interassay coefficients of variation were 6.5% and 10.4%, respectively. Total cholesterol, triglyceride, HDL-C, and LDL-C levels

were determined by enzymatic methods using a model 747 automated clinical chemistry analyzer (Hitachi, Tokyo, Japan). Homeostasis model assessment of insulin resistance index was calculated using the formula (fasting insulin [ $\mu\text{IU/mL}$ ]  $\times$  fasting glucose [ $\text{mmol/L}$ ] / 22.5), and quantitative insulin sensitivity check index was calculated as  $1 / (\log \text{fasting insulin } [\mu\text{IU/mL}] + \log \text{fasting glucose } [\text{mg/dL}])$ .

Serum levels of adiponectin, interleukin-6 (IL-6), soluble vascular cellular adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), monocyte chemotactic protein-1 (MCP-1), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were measured using a MILLIPLEX<sup>™</sup> Human Cytokine/Chemokine panel (Millipore, Billerica, MA). Intra- and interassay coefficients of variation were 9.2 and 15.9% for adiponectin, 8.1 and 11.6% for IL-6, 4.5 and 8.5% for sVCAM-1, 7.9 and 9.7% for sICAM-1, 6.1 and 12.0% for MCP-1, and 10.5 and 15.9% for TNF- $\alpha$ , respectively.

### Statistical analysis

SAS PROC MIXED (SAS Institute, Cary, NC) was used to analyze the data from the crossover trial. The Grizzles model included treatment effect, carry-over effect, and sequential effect as fixed effects and the subject effect as a random effect. The model was fitted for seven different



**Figure 1** Trial design.

**Table 1 Baseline characteristics of participants (n = 37)**

Characteristic	Mean ± SD (or N/%)
Age (years)	61.2 ± 6.7
Male sex (n/%)	15 (40.5%)
Duration of diabetes (years)	10 ± 6
Hypertension	32 (86.5%)
Dyslipidemia	14 (37.8%)
Current smoker	13 (35.1%)
BMI (kg/m <sup>2</sup> )	26.2 ± 2.9
Waist circumference (cm)	92.5 ± 8.0
Systolic blood pressure (mmHg)	131.9 ± 11.8
Diastolic blood pressure (mmHg)	79.2 ± 11.4
Fasting glucose (mg/dL)	133.4 ± 27.1
HbA1c (%)*	7.1 ± 1.1
Fasting insulin (μU/mL)*	11.6 ± 1.6
HOMA-IR*	3.8 ± 1.6
QUICKI	0.32 ± 0.02
Total cholesterol (mg/dL)	155.2 ± 25.2
Triglyceride (mg/dL)*	131.1 ± 1.7
HDL-C (mg/dL)	46.2 ± 9.9
LDL-C (mg/dL)	91.6 ± 21.2
hsCRP (mg/L)*	1.07 ± 2.65
Mean baPWV (cm/sec)	1591.4 ± 192.6
Adiponectin (ng/mL)*	8.86 ± 1.87
IL-6 (pg/mL)*	3.99 ± 2.94
TNF-α (ng/dL)*	6.36 ± 1.27
MCP-1 (ng/dL)*	590.2 ± 1.63
sVCAM-1 (ng/dL)	1224.4 ± 267.6
sICAM-1 (ng/dL)*	169.7 ± 1.29

*HOMA-IR*, homeostasis model assessment of insulin resistance, *QUICKI* quantitative insulin sensitivity check index, *hsCRP* high sensitivity C-reactive protein, *baPWV* brachial-ankle pulse wave velocity, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-alpha, *MCP-1* monocyte chemoattractant protein-1, *sVCAM-1* soluble vascular cellular adhesion molecule-1, *sICAM-1* soluble intercellular adhesion molecule-1.

Data are presented as the mean ± SD. \*Geometric mean ± SD.

responses (baPWV, IL-6, TNF-α, adiponectin, MCP-1, sVCAM-1, and sICAM-1). There were no significant carry-over and sequential effects. Baseline characteristics of study participants were comparable in both groups and both phases. Primary outcome was change in arterial stiffness measured by baPWV. Secondary outcome was change in inflammatory markers. The sample size of the study was determined on the basis of the estimation for the primary outcome of baPWV from previous trials [18,19]. Using a two-sided test for differences in independent binomial proportions with an alpha level of 0.05, 36 patients would have to undergo randomization for the study to have 80% power to detect a difference in the baPWV between the two study arms. Therefore, at

least 48 patients were enrolled to account for an anticipated 25% loss in follow-up. The level of significance was 0.05. All analyses were performed using SAS version 9.1.3 (SAS Institute).

## Results

Forty five participants were randomly assigned to each study arm. Two participants withdrew their consent for participation before the first treatment phase and one participant withdrew during the washout period. During the first phase, two patients in the cilostazol arm withdrew due to headache ( $n = 1$ ) and dizziness ( $n = 1$ ). After completion of cilostazol treatment, three patients withdrew due to headache ( $n = 2$ ) and dizziness ( $n = 1$ ). As a result, 37 participants completed the full protocol (Figure 1). Throughout the study period, the medications were generally well tolerated by the 37 subjects. One participant experienced mild headaches but completed the study.

Table 1 summarizes the baseline characteristics of the participants. The subjects comprised 15 males (40.5%) and the mean age of the total participants was  $61.2 \pm 6.7$  years. The mean duration of diabetes was  $10 \pm 6$  years and the mean BMI was  $26.2 \pm 2.9$  kg/m<sup>2</sup>. The anthropometric and biochemical data showed that, for most participants, diabetes was generally well-controlled. The mean glycated hemoglobin (HbA1c) level was 7.1%, mean systolic and diastolic pressure was 131.9 and 79.2 mmHg, respectively, mean total cholesterol was 155.2 mg/dL, and mean LDL cholesterol was 91.6 mg/dL.

Table 2 shows changes from baseline to week 8 of anthropometric and metabolic parameters in both comparison groups. Baseline parameters were not significantly different in both groups. After the 8-week treatment with cilostazol or placebo, no anthropometric measure had changed substantially. However, WC in the cilostazol group significantly decreased from 92.6 to 91.4 cm ( $P = 0.007$ ). Lipid profiles including total cholesterol, triglyceride, and HDL-C improved in both groups, but none of the improvements was statistically significant. Cilostazol treatment lowered mean baPWV from  $1621.8 \pm 229.8$  to  $1592.0 \pm 249.3$  cm/sec, but the decrease was not statistically significant. Most of inflammatory markers including adiponectin, IL-6, MCP-1, sVCAM-1, and sICAM-1 showed tendency of improvement with cilostazol. However, there was significant change only in sVCAM-1 level ( $1288.7 \pm 285.6$  to  $1168.2 \pm 252.3$  ng/dL,  $P = 0.0003$ ) and a modest change in serum adiponectin level ( $9.17 \pm 1.88$  to  $9.92 \pm 1.93$  ng/mL,  $P = 0.07$ ). There were no significant changes of outcomes in the placebo group except IL-6 ( $4.13 \pm 3.14$  to  $3.21 \pm 3.34$  pg/mL,  $P = 0.02$ ).

Comparing the effect of cilostazol and placebo on the outcomes, cilostazol significantly reduced sVCAM-1 level

**Table 2 Changes from baseline to week 8 of anthropometric and metabolic parameters in cilostazol and placebo group (n=37)**

	Placebo			Cilostazol		
	Baseline	Follow-up	P-value	Baseline	Follow-up	P-value
BMI (kg/m <sup>2</sup> )	26.2 ± 2.9	26.2 ± 2.9	0.29	26.2 ± 2.9	26.0 ± 2.9	0.12
Waist circumference (cm)	92.5 ± 8.0	92.1 ± 7.6	0.36	92.6 ± 8.0	91.4 ± 7.4	0.007
Systolic blood pressure (mmHg)	131.0 ± 10.8	131.1 ± 12.0	0.93	130.6 ± 11.2	129.6 ± 13.0	0.59
Diastolic blood pressure (mmHg)	79.6 ± 11.2	81.3 ± 10.3	0.35	79.4 ± 9.8	77.4 ± 9.3	0.20
Fasting glucose (mg/dL)	129.2 ± 22.2	129.6 ± 32.0	0.94	137.5 ± 41.2	140.2 ± 31.7	0.66
HbA1c (%) <sup>*</sup>	7.2 ± 1.2	7.1 ± 1.2	0.19	7.3 ± 1.2	7.2 ± 1.2	0.42
Fasting insulin (μU/mL) <sup>*</sup>	11.0 ± 1.6	11.0 ± 1.6	0.99	11.1 ± 1.5	10.3 ± 1.5	0.21
HOMA-IR <sup>*</sup>	3.5 ± 1.6	3.6 ± 1.7	0.50	3.6 ± 1.6	3.5 ± 1.6	0.73
QUICKI	0.32 ± 0.02	0.32 ± 0.02	0.59	0.32 ± 0.02	0.32 ± 0.02	0.74
Total cholesterol (mg/dL)	156.7 ± 24.2	154.1 ± 23.6	0.49	157.9 ± 21.0	154.9 ± 23.0	0.39
Triglyceride (mg/dL) <sup>*</sup>	143.9 ± 1.7	140.7 ± 1.6	0.77	134.6 ± 1.6	121.9 ± 1.5	0.19
HDL-C (mg/dL)	43.0 ± 9.3	44.7 ± 13.1	0.37	47.1 ± 11.0	48.1 ± 10.9	0.41
LDL-C (mg/dL)	94.1 ± 21.6	90.3 ± 19.9	0.28	93.9 ± 19.9	88.9 ± 20.0	0.10
hsCRP (mg/L) <sup>*</sup>	1.09 ± 2.78	0.93 ± 3.28	0.39	0.90 ± 2.79	1.15 ± 2.24	0.09
Mean baPWV (cm/sec)	1597.9 ± 239.6	1606.7 ± 259.6	0.77	1621.8 ± 229.8	1592.0 ± 249.3	0.35
Adiponectin (ng/mL) <sup>*</sup>	8.44 ± 1.82	8.53 ± 1.95	0.72	9.17 ± 1.88	9.92 ± 1.93	0.07
IL-6 (pg/mL) <sup>*</sup>	4.13 ± 3.14	3.21 ± 3.34	0.02	4.33 ± 3.28	3.41 ± 2.48	0.74
TNF-α (ng/dL) <sup>*</sup>	6.66 ± 1.32	6.12 ± 1.36	0.07	6.42 ± 1.32	6.36 ± 1.37	0.87
MCP-1 (ng/dL) <sup>*</sup>	546.6 ± 1.43	577.5 ± 1.38	0.32	588.1 ± 1.57	570.4 ± 1.43	0.67
sVCAM-1 (ng/dL)	1227.6 ± 274.0	1225.1 ± 281.4	0.94	1288.7 ± 285.6	1168.2 ± 252.3	0.0003
sICAM-1 (ng/dL) <sup>*</sup>	158.4 ± 1.38	156.3 ± 1.39	0.70	155.2 ± 1.38	144.0 ± 1.35	0.10

HOMA-IR homeostasis model assessment of insulin resistance, QUICKI quantitative insulin sensitivity check index, hsCRP high sensitivity C-reactive protein, baPWV brachial-ankle pulse wave velocity, IL-6 interleukin-6, TNF-α tumor necrosis factor-alpha, MCP-1 monocyte chemoattractant protein-1, sVCAM-1 soluble vascular cellular adhesion molecule-1, sICAM-1 soluble intercellular adhesion molecule-1.

Data are presented as the mean ± SD.

<sup>\*</sup>Geometric mean ± SD, statistical significance was estimated after logarithmic transformation.

P-value were obtained using paired t-test based on change (follow-up-baseline) in each group.

(mean difference 105.18 ng/dL, 95% CI 10.65 to 199.71) compared with placebo (Table 3). However, there were no differences observed in baPWV, hsCRP, adiponectin, IL-6, TNF-α, MCP-1, and sICAM-1 between the cilostazol and placebo groups.

## Discussion

To the best of our knowledge, this is the first randomized controlled trial comparing the effect of cilostazol and placebo on arterial stiffness and biochemical markers related to vascular inflammation including vascular cellular adhesion molecules in diabetic patients without established CVD. Cilostazol treatment for 8 weeks did not substantially change PWV compared with placebo in patients with type 2 diabetes and metabolic syndrome. However, there was significant reduction of serum sVCAM-1 level, and modest improvement of serum adiponectin level with cilostazol treatment.

Arterial stiffness primarily represents elastic property of arteries and has a role in the development of CVD.

Various simple and noninvasive methods measuring arterial stiffness have been suggested and PWV is the most widely-used method in the clinical setting. Among various methods of measurement of PWV, baPWV correlates well with carotid-femoral PWV and aortic PWV [20,21], and has been closely associated with incident hypertension [22], insulin resistance [23], and coronary atherosclerosis [24].

Initially, we hypothesized that cilostazol would improve arterial stiffness. Cilostazol is a phosphodiesterase 3 inhibitor; this inhibition and associated increase in cAMP in platelets and vascular smooth muscle cells contributes to the antiplatelet and vasodilatory effects of cilostazol [25]. In several clinical trials, cilostazol treatment attenuated the increase of carotid IMT compared with placebo group in type 2 diabetic patients [13,26]. Recently, the Diabetic Atherosclerosis Prevention by Cilostazol study found that cilostazol more potently inhibited progression of carotid IMT in diabetic patients, even compared with aspirin [12]. In addition,



**Table 3 Effect of cilostazol vs. placebo on anthropometric and metabolic parameters**

	Mean difference	95% CI for the difference	P-value
BMI (kg/m <sup>2</sup> )	0.29	-0.03 to 0.61	0.08
Waist circumference (cm)	0.88	-0.28 to 2.03	0.13
Systolic blood pressure (mmHg)	0.76	-4.95 to 6.47	0.79
Diastolic blood pressure (mmHg)	3.07	-1.75 to 7.90	0.21
Fasting glucose (mg/dL)	-3.60	-17.04 to 9.84	0.59
HbA1c (%) <sup>*</sup>	-0.01	-0.05 to 0.03	0.53
Fasting insulin (μU/mL) <sup>*</sup>	0.07	-0.12 to 0.25	0.45
HOMA-IR <sup>*</sup>	0.06	-0.17 to 0.29	0.59
QUICKI	-0.00	-0.01 to 0.01	0.70
Total cholesterol (mg/dL)	-1.21	-11.46 to 9.05	0.81
Triglyceride (mg/dL) <sup>*</sup>	0.05	-0.15 to 0.26	0.61
HDL-C (mg/dL)	0.98	-3.54 to 5.51	0.66
LDL-C (mg/dL)	-0.71	-9.65 to 8.24	0.87
hsCRP (mg/L) <sup>*</sup>	-0.38	-0.84 to 0.09	0.11
Mean baPWV (cm/sec)	31.42	-55.67 to 118.50	0.47
Adiponectin (ng/mL) <sup>*</sup>	-0.07	-0.17 to 0.03	0.16
IL-6 (pg/mL) <sup>*</sup>	-0.18	-0.61 to 0.26	0.38
TNF-α (ng/dL) <sup>*</sup>	-0.08	-0.22 to 0.06	0.27
MCP-1 (ng/dL) <sup>*</sup>	0.08	-0.11 to 0.27	0.41
sVCAM-1 (ng/dL)	105.18	10.65 to 199.71	0.03
sICAM-1 (ng/dL) <sup>*</sup>	0.06	-0.05 to 0.18	0.28

*HOMA-IR* homeostasis model assessment of insulin resistance, *QUICKI*, quantitative insulin sensitivity check index, *hsCRP* high sensitivity C-reactive protein, *baPWV* brachial-ankle pulse wave velocity, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-alpha, *MCP-1* monocyte chemoattractant protein-1, *sVCAM-1* soluble vascular cellular adhesion molecule-1, *sICAM-1* soluble intercellular adhesion molecule-1.

Mean difference = placebo-cilostazol.

<sup>\*</sup>Statistical significance was estimated after logarithmic transformation.

cilostazol increased mean ankle blood flow in patients with arteriosclerosis obliterans [27], and increased coronary flow reserve in patients with coronary artery disease [28].

The present results did not prove the efficacy of cilostazol to improve the arterial stiffness. Although the mean baPWV was slightly decreased with cilostazol and increased with placebo, there was no significant difference between the two groups. There are several possible explanations for this result. First, the study period might not have been long enough. Although there is no established study period for which a clinical outcome becomes apparent, the present study was a relatively short study period compared with other studies involving cilostazol. Second, most of the patients (31 of 37 subjects; 83.7%) had already undergone treatment with angiotensin-converting enzyme inhibitor or angiotensin II receptor blockade, and a considerable number of participants already had taken statins (14 of 37 subjects; 37.8%) because we wanted to investigate the additional effect of cilostazol in a real clinical setting. So, it is possible that further improvement with cilostazol treatment might not be noted due to these drugs that might already affect arterial stiffness. Indeed, in a

subgroup analysis, except for the subjects using statins, the effect of cilostazol was more prominent, although not statistically significant (data not shown).

The antiatherogenic and antiinflammatory effects of cilostazol may be come from cAMP-mediated increase in lipoprotein lipase and inhibition of cytokine production. An in vivo study reported cilostazol-associated increase in cardiac lipoprotein lipase in streptozotocin-induced diabetic rats [11]. Cilostazol also significantly reduced the increased TNF-α production induced by lipopolysaccharide in human umbilical vein endothelial cells [29]. In addition, recent in vitro studies found that cilostazol reduced the expression of VCAM-1 and MCP-1 and activate the production of nitric oxide [30,31]. In clinical studies, cilostazol treatment decreased P2Y<sub>12</sub> reactivity index as a marker of platelet function [32], also decreased hsCRP and soluble CD40 ligand levels, and increased adiponectin level in diabetic patients with peripheral arterial occlusion disease [14].

This study is the first clinical study that proved the beneficial effect of cilostazol on sVCAM-1 level, and adds to the evidence to the clinically-apparent anti-inflammatory role of cilostazol. VCAM-1 and ICAM-1

belong to the immunoglobulin gene superfamily and function as endothelial ligands for integrins. Previous studies suggested that VCAM-1 has a role in the recruitment of leukocytes in early atherosclerotic lesions via interaction with VLA-4 integrins on monocytes and lymphocytes [33,34]. Higher levels of soluble VCAM-1 have been documented in subjects with type 2 diabetes [35], metabolic syndrome [36], and atherosclerosis [37], and have been associated with increased CVD mortality [4]. A clinical study showed reduced sVCAM-1 levels in obese women after weight loss over 1-year [38]. Presently, cilostazol modestly decreased IL-6, MCP-1, and sICAM-1 levels in addition to sVCAM-1 with short term treatment. These findings indicate that cilostazol might have an anti-inflammatory role in the early phase of atherosclerosis progression, and it is conceivable that cilostazol could improve other inflammatory markers with a longer treatment period.

Several limitations of our study must be acknowledged. First, this study was confined to type 2 diabetic patients with metabolic syndrome, and results from this study should not be extrapolated to other patient populations. Secondly, our study was performed using a small number of patients over a short period of time. Whether the observed effect of cilostazol on serum sVCAM-1 level in these patients translates into cardiovascular outcomes should be evaluated by a long-term, large scale, randomized, multicenter study. Third, we did not measure other markers related to platelet function or platelet activation such as soluble CD40 ligand, which might be helpful for assessment and interpretation of the effects of cilostazol on vascular inflammation.

## Conclusion

Despite of its potential favorable effects on arterial stiffness, treatment with cilostazol for 8 weeks did not improve the mean baPWV compared with placebo treatment in diabetic patients with metabolic syndrome but not having established CVD. However, this short term treatment was associated with significant reduction of sVCAM-1 level, and modest improvement of adiponectin level. We could not exclude the possibility that cilostazol would improve the vascular outcomes over a longer time. Further studies are needed to elucidate the distinct effects of cilostazol in type 2 diabetes, especially with long-term treatment.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

NHK and HYK wrote the manuscript and researched data. HA contributed to the data analysis. SGK researched data, reviewed and edited the manuscript. JAS, NHK, KMC, SHB, and DSC contributed to the discussion and reviewed the manuscript. All authors read and approved the final manuscript.

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