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Original Article

The Effect of Cilostazol on Endothelial Function as Assessed by Flow-Mediated Dilation in Patients with Coronary Artery Disease

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***Aim*: The vascular endothelium plays a key role in the pathophysiology of atherosclerosis. Flow-mediated dilation (FMD) is a novel way of assessing endothelial function. Cilostazol is a unique antiplatelet drug that also has the potential to improve endothelial function. The objective of this present study was to investigate the effects of cilosatzol on endothelial function as assessed by FMD.**

***Methods*: Fifty-one patients with coronary artery disease (CAD) were assigned to one of two groups: the Cilostazol(+) group (with cilostazol) and Cilostazol(−) group (without cilostazol). In addition to conventional dual antiplatelet therapy with aspirin and clopidogrel/ticlopidine, the Cilostazol(+) group ($n=27$) was also given cilostazol (100 mg/day). The Cilostazol(−) group ($n=24$) did not receive cilostazol. FMD was assessed at enrollment and after 6–9 months.**

***Results*: The FMD of both the Cilostazol(+) and Cilostazol(−) groups remained similar at 5.2 (interquartile range: 3.8–8.5) to 5.4 (interquartile range: 4.2–6.7) ($P=0.29$) and 5.0 (interquartile range: 3.6–6.4) to 4.9 (interquartile range: 4.0–7.0) ($P=0.38$), respectively. However, the diameters of the baseline and maximal brachial arteries tended to increase in the Cilostazol(+) group (baseline: 4.2 ± 0.7 to 4.4 ± 0.7, $P=0.18$; maximal: 4.5 ± 0.7 to 4.6 ± 0.7 $P=0.22$), whereas that of the Cilostazol(−) group tended to decrease (baseline: 4.1 ± 0.6 to 3.9 ± 0.5, $P=0.10$; maximal: 4.3 ± 0.7 to 4.1 ± 0.5, $P=0.05$). The rates of change in the baseline diameter (Cilostazol(+): $3.7\pm9.8\%$ vs. Cilostazol(−): $-3.8\pm12.2\%$, $P=0.03$) and maximal diameter (Cilostazol(+): $+3.1\pm8.9\%$ vs. Cilostazol(−): $-4.4\pm12.0\%$, $P=0.02$) were significantly different.**

***Conclusion*: Although cilostazol didn't affect the FMD, there was a significant difference in the rates of change in baseline and maximal brachial artery diameter. This may have a beneficial effect in patients with cardiovascular disease.**

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Key words: Cilostazol, Endothelial Function, Flow-mediated dilation, Coronary artery disease

Introduction

Cardiovascular disease (CVD) is the number one cause of death throughout the world[1]. The World Health Organization (WHO) reported that an estimated 17.5 million people died from CVD in 2012, which represented 31% of global deaths. Among these deaths, an estimated 7.4 million people died due to coronary artery disease (CAD), while 6.7 million died due to stroke. In contrast, in 2000, an estimated 6 million died due to CAD, while 5.7 million died due to stroke. Accordingly, the number of deaths caused by CVDs has increased over the past decade. It is therefore essential to elucidate the endothelial functions that play a key role in the pathophysiology of atherosclerosis.

The endothelium is not only a passive barrier but also an active transducer, as it participates in a variety of paracrine factors that act locally in the blood vessel walls and lumen[2]. Under healthy conditions, the endothelium produces a wide range of factors that regulate vascular tone, adhesion of circulating blood

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cells to the vessel wall, thrombus formation, smooth muscle cell proliferation, and vessel wall inflammation. However, under the existence of risk factors such as hypercholesterolemia, hypertension, smoking, and diabetes mellitus, the phenotype of the endothelium may be altered such that it accelerates inflammation, thrombosis, vasoconstriction, and the formation of atherosclerotic lesions[3]. This maladaptive endothelial phenotype appears in early atherosclerosis and is associated with the classical cardiovascular risk factors.

The flow-mediated dilation (FMD) test has emerged as a major non-invasive tool for assessing endothelial function in clinical settings[4-6]. FMD acts as a marker of Nitric Oxide (NO)-mediated endothelium-dependent vasodilator function. Impaired FMD is an indicator of endothelial dysfunction and is reported to be a predictor of future CVD[7, 8]. The FMD value has also been found to be a predictor of changes in the levels of carotid plaque, independent of the classical cardiovascular risk factors[9]. Because endothelial dysfunction is a systemic process, an impaired FMD measurement in the forearm indicates the presence of systemic endothelial dysfunction. Thus, impaired FMD is an early marker of atherosclerosis. Notably, FMD has been shown to be strongly correlated with coronary endothelial function[10].

Cilostazol is a unique antiplatelet drug that selectively and reversibly targets phosphodiesterase Ⅲ (PDE-Ⅲ)[11]. PDE-Ⅲ is usually present in the platelets, endothelial cells, and smooth muscle cells, where it increases cyclic adenosine monophosphate concentrations, resulting in vasodilation. It also increases sensitivity to endogenous vasodilators, such as prostaglandins, and inhibits both the primary and secondary platelet aggregation induced by collagen, adenosine diphosphate (ADP), arachidonic acid, and epinephrine. Cilostazol is also reported to reduce angiographic restenosis after percutaneous transluminal angioplasty with provisional nitinol stenting for femoropopliteal lesions[12]. Additionally, the clinical outcomes of patients with acute myocardial infarction who are treated with cilostazol, in addition to conventional dual antiplatelet therapy, are favorable in comparison to those who are treated with conventional dual antiplatelet therapy[13].

Aim

Although FMD has been well assessed and cilostazol has been widely used in patients with atherosclerosis, the effect of cilostazol on endothelial function as assessed by FMD has not been elucidated in patients with coronary artery disease. The present study was therefore performed to investigate the effect of cilostazol on endothelial function as assessed by FMD in patients with coronary artery disease.

Methods

Study Subjects

This study was a prospective, open-label, randomized trial. Patients were eligible if they had angina requiring percutaneous coronary intervention (PCI) within two months prior to enrollment. The exclusion criteria included heart failure (New York Heart Association functional class Ⅱ—Ⅳ), left ventricular ejection fraction $<40\%$, end-stage renal failure requiring hemodialysis, atrial fibrillation, active systemic inflammatory disease, collagen disease, active hepatic disease, malignancy, the usage of anticoagulation therapy, and a history of acute myocardial infarction within the last 3 months. A total of 51 eligible patients were prospectively recruited from September 2010 to March 2012 at Showa University Fujigaokoa Hospital. The patients were randomly assigned to either the Cilostazol(+) group (with cilostazol) or the Cilostazol(−) group (without cilostazol). On top of conventional dual antiplatelet therapy (DAPT) with aspirin (100 mg/day) and clopidogrel (75 mg/day)/ticlopidine (200 mg/day), the patients in the Cilostazol(+) group ($n=27$) were given cilostazol (100 mg/day). The patients in the Cilostazol(−) group ($n=24$) were not given cilostazol. The patients' endothelial function and blood biochemistry were assessed at enrollment and at 6–9 months after the start of the study. In all patients, coronary risk factors were controlled according to Japanese circulation guidelines[14, 15]. Clinical follow-up visits were scheduled every 1–3 months. At the time of enrollment and 6 to 9 months after enrollment, all of the patients underwent endothelial function and blood biochemistry assessments. Routine angiographic follow-up was not mandatory. All adverse clinical events were assessed.

This study was approved by the Institutional Ethics Review Committee. Written informed consent was obtained from each patient before participation. This study was registered under the UMIN protocol registration system (ID UMIN 000004065).

The Assessment of Endothelial Function

All subjects were instructed to fast after dinner on the day before the assessment and to refrain from smoking and ingesting any alcohol or caffeine during the study period. All assessments were conducted from 9 to 10:30 AM. All subjects rested for at least 15 min in a seated position in a quiet, dark, air-conditioned room before each FMD assessment. A longitudinal image of the brachial artery was recorded at baseline

using an ultrasound with a 10M-Hz linear array transducer probe (UNEX, Nagoya, Japan). A forearm-cuff was then inflated for 5 min at 50 mmHg above the SBP (systolic blood pressure) just before the FMD assessment. After deflation of the cuff, the diastolic diameter of the brachial artery was semi-automatically recorded continuously for 2 min. The FMD was then estimated as the percent change in vessel diameter from baseline to maximum dilatation during reactive hyperemia. Because FMD is highly dependent on the baseline diameter of the vessel, we also compared the baseline and maximal diameters in each group. Experienced technicians were blinded to the clinical data of the study participants. Intra- and inter-observer correlation coefficients for FMD were considerably high (0.99 and 0.92, respectively).

The Assessment of Angiography

Lesion characteristics were assessed according to AHA classification. Drug eluting stent (DES) usage, stent diameter and length, the number of stents, and the number of stents per vessel were described. Target lesion revascularization (TLR) and target vessel revascularization (TVR) were assessed.

Blood Biochemistry

Blood samples were collected from all patients after overnight fasting at baseline and at 6–9 months. High-sensitive C-reactive protein (CRP) tests were conducted by SRL, Inc (Tokyo, Japan). Health Sciences Research Institute, Inc. (Yokohama, Japan) assessed the levels of brain natriuretic peptide (BNP). All other biochemical analyses were performed in-house.

Statistical Analyses

All statistical analyses were performed using the JMP software program (JMP, Version 11; SAS Institute Inc., NC, USA). The sample size was calculated by a power analysis using preliminary data with the following assumptions: a Type I error of 0.05 (2-tailed), 80% power, a mean increase in FMD of 10% in the Cilostazol(+) group, a mean increase in FMD of 0% in the Cilostazol(−) group, and a standard deviation of 10% in each group. It was determined that a minimum of 17 patients (total of 34 patients) would be required to obtain 80% power in detecting a difference in the %change of FMD from enrollment to 6–9 months.

The patients' age, laboratory data, baseline brachial artery diameter, and maximal brachial artery diameter were expressed as the mean ± SD. The stent diameter, stent length, stent number, stent number per lesion, and FMD were expressed as the median (interquartile range). Comparisons between continuous variables were analyzed using either the *t*-test or Wilcoxon's rank sum test, as appropriate. The categorical variables were analyzed using the chi-square test. The enrollment and follow-up data were compared using a paired *t*-test or Wilcoxon's singed rank test, as appropriate. *P* values of <0.05 were considered to be statistically significant.

Results

Patient disposition is summarized in **Fig. 1**. Fifty-one patients were randomly assigned to the Cilostazol(+) ($n=27$) and Cilostazol(−) groups ($n=24$). All of the patients survived for the duration of the study period. In the Cilostazol(+) group, cilostazol treatment was stopped in 2 patients due to palpitation and 1 patient due to minor bleeding; we could not follow 2 patients due to poor compliance. In the Cilosatazol(−) group, we could not follow 2 patients due to poor compliance. There was no single major bleeding episode. Accordingly, the final analysis included 22 patients in the Cilostazol(+) group and 22 patients in the Cilostazol(−) group.

Table 1 shows the baseline clinical characteristics of the study patients. There were no significant differences in terms of age, gender, hypertension, hyperlipidemia, diabetes, chronic kidney disease, current smoking status, cerebrovascular disease, peripheral artery disease, previous myocardial infarction or unstable angina pectoris. There were no statistically significant differences between the two groups with regard to the use of major medications, including angiotensin converting enzyme inhibitor (ACE-I)/angiotensin Ⅱ receptor blockers (ARBs), β-blockers, calcium channel blockers (CCB), statins and nitrate/nicorandil.

The procedural characteristics are shown in **Table 2**. We did not observe any significant differences in the number of treated lesions, type B2 or C lesions, target vessel location, indications of *de novo* lesions, indications of in-stent restenosis, prevalence of previous PCI, prevalence of previous CABG or drug eluting stent (DES) usage. Regarding stent usage, the diameter, length, number of stents, and number of stents per lesion were similar. At 6–9 months, target vessel and target lesion revascularization was comparable between the two groups.

Table 3 shows the laboratory data at enrollment and at 6–9 months in each group. Upon enrollment, all laboratory data were comparable between the two groups. There were no significant differences in serum creatinine, LDL cholesterol, triglyceride, or glycohemoglobin levels over time in either group. In both groups, the level of HDL cholesterol increased over

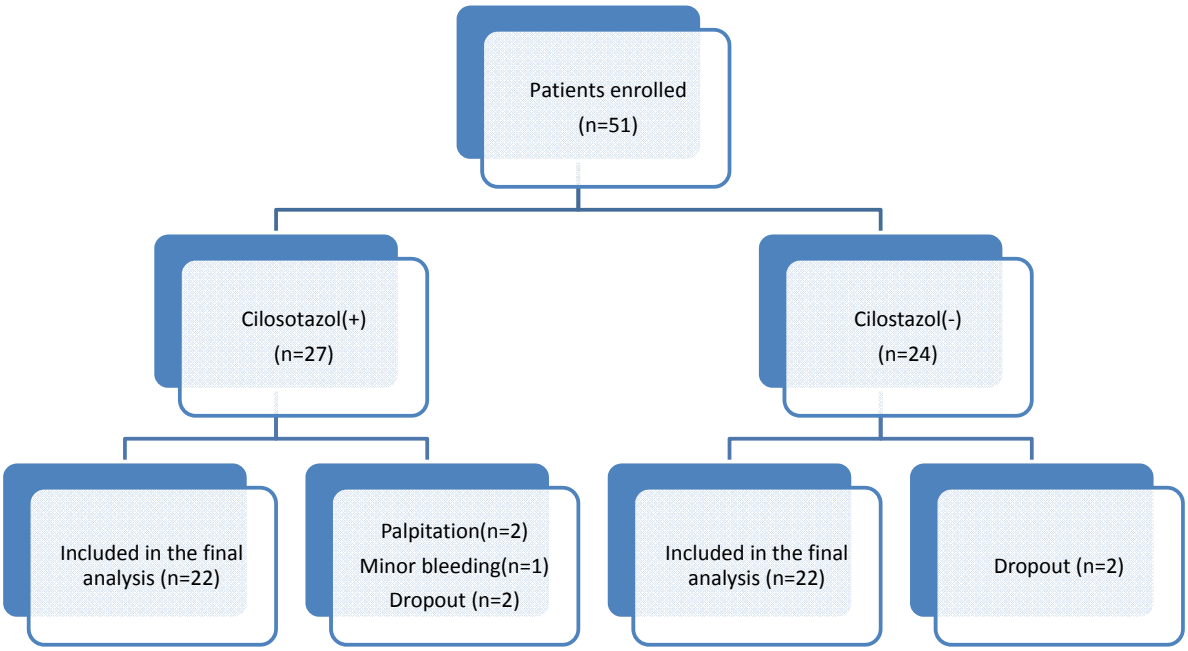

Fig. 1. Patient disposition flow chart

Table 1. The baseline clinical characteristics of patients

	Overall ($n=44$)	Cilostazol (+) ($n=22$)	Cilostazol (−) ($n=22$)	P value
Age, years	67 ± 8	67 ± 7	66 ± 10	0.81
Male, *n* (%)	34 (77.3%)	16 (72.7%)	18 (81.8%)	0.47
Hypertension, *n* (%)	32 (72.7%)	18 (81.8%)	14 (63.6%)	0.18
Hyperlipidemia, *n* (%)	38 (86.4%)	19 (86.4%)	19 (86.4%)	1.00
Diabetes, *n* (%)	19 (43.2%)	10 (45.5%)	9 (40.9%)	0.76
CKD, *n* (%)	5 (11.4%)	1 (4.6%)	4 (18.1%)	0.15
Current Smoker, *n* (%)	13 (29.6%)	5 (22.7%)	8 (36.3%)	0.32
CVD, *n* (%)	2 (4.6%)	0	2 (9.1%)	0.15
PAD, *n* (%)	1 (2.3%)	0	1 (4.6%)	0.31
Previous MI	10 (22.7%)	5 (22.7%)	5 (22.7%)	1.00
UAP, *n* (%)	16 (38.4%)	6 (37.5%)	10 (45.5%)	0.21
Medication, *n* (%)				
ACE-I/ARB	26 (59.1%)	14 (63.6%)	12 (54.6%)	0.54
β-blokers	13 (29.6%)	4 (18.2%)	9 (40.9%)	0.10
CCB	19 (43.2%)	11 (50.0%)	8 (36.4%)	0.36
Statin	40 (90.9%)	19 (86.4%)	21 (95.5%)	0.29
Nitrate/Nicorandil	7 (15.9%)	5 (22.7%)	2 (9.1%)	0.22

The data are shown as the mean ± SD or *n* (%). CKD, chronic kidney disease; CVD, cerebrovascular disease; PAD, peripheral artery disease; Previous MI, previous myocardial infarction; EF, ejection fraction; UAP, unstable angina pectoris; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker.

time; a significant difference was only observed in the Cilostazol(−) group. The LDL/HDL ratio significantly decreased over time in both groups. BNP decreased significantly in the Cilostazol(+) group. BNP also decreased in the Cilostazol(−) group, but these data were not statistically significant. High-sensitive CRP levels were assessed in a limited number of patients (Cilostazol(+) group, $n=19$; Cilostazol(−)

Table 2. The characteristics of the procedures

	Overall ($n=44$)	Cilostazol (+) ($n=22$)	Cilostazol (−) ($n=22$)	*P* value
Number of treated lesions, *n* (%)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.87
Target Vessel, *n* (%)				
LMT	2 (4.6%)	1 (4.6%)	1 (4.6%)	1.00
RCA	18 (40.9%)	10 (45.5%)	8 (36.4%)	0.54
LAD	32 (72.7%)	16 (72.7%)	16 (72.7%)	1.00
LCX	14 (31.8%)	6 (27.3%)	8 (36.4%)	0.52
De novo, *n* (%)	41 (93.2%)	22 (100.0%)	19 (86.4%)	0.07
ISR, *n* (%)	8 (18.2%)	4 (18.2%)	4 (18.2%)	1.00
Type B2 or C, *n* (%)	12 (27.3%)	6 (27.3%)	6 (27.3%)	1.00
Previous PCI, *n* (%)	11 (25%)	7 (31.8%)	4 (18.2%)	0.30
Previous CABG, *n* (%)	1 (2.3%)	1 (4.6%)	0 (0%)	0.31
DES usage, *n* (%)	35 (79.6%)	19 (86.4%)	16 (72.8%)	0.26
Stent diameter, mm	3.0 (3.0-3.5)	3.0 (2.75-3.5)	3.5 (3-3.5)	0.48
Stent length, mm	18 (15-23)	18.0 (15.0-23.0)	18.0 (14.0-23.0)	0.78
Stent number, *n*	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.5 (1.0-2.3)	0.66
Stent number per vessel, *n*	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.62
TVR (6-9 months), *n* (%)	9 (20.5%)	5 (22.7%)	4 (18.2%)	0.71
TLR (6-9 months), *n* (%)	7 (15.9%)	4 (18.2%)	3 (13.6%)	0.68

Data are *n* (%) or median and (interquartile range). LMT, left main trunk; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; ISR, in-stent restenosis; Previous PCI, previous percutaneous coronary intervention; Previous CABG, previous coronary artery bypass graft; DES, drug-eluting stent; TLR, target lesion revascularization; TVR target vessel revascularization.

Table 3. Laboratory data of patients at enrollment and at 6–9 Months

	Cilostazol (+) ($n=22$)			Cilostazol (−) ($n=22$)		
	Enrollment	At 6-9 months	*P*-value	Enrollment	At 6-9 months	*P*-value
Cre, mg/dl	0.81 ± 0.14	0.82 ± 0.17	0.33	0.88 ± 0.24	0.87 ± 0.27	0.37
LDL cholesterol, mg/dl	110 ± 27	103 ± 24	0.30	102 ± 35	90 ± 28	0.16
HDL cholesterol, mg/dl	54 ± 18	58 ± 20	0.07	50 ± 10	53 ± 11	0.01
LDL/HDL ratio	2.2 ± 1.1	2.0 ± 0.9	0.01	2.1 ± 0.8	1.8 ± 0.8	0.02
TG, mg/dl	134 ± 52	130 ± 50	0.56	142 ± 93	156 ± 82	0.53
Hb A1c, %	6.4 ± 0.8	6.6 ± 1.1	0.31	6.7 ± 1.3	6.6 ± 1.2	0.87
BNP, pg/ml	63 ± 121	24 ± 19	0.01	69 ± 96	62 ± 90	0.68

The data are shown as the mean ± SD. Cre, serum creatine; TG, triglyceride; Hb A1c, hemoglobin A1c; BNP, brain natrium peptide.

group, $n=15$). In these patients, high-sensitive CRP levels decreased from 0.29 ± 0.74 mg/dl to 0.12 ± 0.15 mg/dl in the Cilostazol(+) group, but these data were not significant ($P=0.21$), while there was a non-significant increase from 0.19 ± 0.31 mg/dl to 0.32 ± 0.73 mg/dl in the Cilostazol(−) group ($P=0.64$).

Table 4 shows the results of FMD, baseline brachial artery diameter, maximal brachial artery diameter, systolic blood pressure, diastolic blood pressure, and heart rate at each time point. The FMD of both the Cilostazol(+) and Cilostazol(−) groups remained similar at 5.2 (interquartile range:3.8–8.5) to 5.4 (interquartile range:4.2–6.7) ($P=0.29$) and 4.9 (interquartile range:4.0–7.0) to 5.0 (interquartile range: 3.6–6.4) ($P=0.38$), respectively. The percent change in FMD was −6.9% (interquartile range: −23.5–16.6%) in the Clisotazol(+) group and +7.0% (interquartile range: −21.8–49.6%) in the Cilostazol(−) group and was not statistically significant ($P=0.34$). Although the FMD did not change significantly in either group, the baseline brachial artery diameter and maximal brachial artery diameter increased in the Cilostazol(+) group (baseline: 4.2 ± 0.7 to 4.4 ± 0.7, $P=0.18$; maximal: 4.5 ± 0.7 to 4.6 ± 0.7, $P=0.22$) and decreased in

Table 4. FMD (flow-mediated dilation), baseline diameter of brachial artery, maximal diameter of brachial artery, SBP (systolic blood pressure), DBP (diastolic blood pressure), and HR (heart rate) at enrollment and 6–9 months thereafter

	Cilostazol (+) (n = 22)			Cilostazol (−) (n = 22)		
	Enrollment	At 6-9 months	P-value	Enrollment	At 6-9 months	P-value
FMD, %	5.2 (3.8-8.5)	5.4 (4.2-6.7)	0.29	5.0 (3.6-6.4)	4.9 (4.0-7.0)	0.38
baseline diameter, mm	4.2 ± 0.7	4.4 ± 0.7	0.18	4.1 ± 0.6	3.9 ± 0.5	0.10
maximal diameter, mm	4.5 ± 0.7	4.6 ± 0.7	0.22	4.3 ± 0.7	4.1 ± 0.5	0.05
SBP, mmHg	125 ± 16	131 ± 16	0.15	125 ± 17	130 ± 19	0.28
DBP, mmHg	69 ± 7	73 ± 11	0.21	69 ± 13	70 ± 10	0.74
HR, n/min	67 ± 11	65 ± 12	0.64	70 ± 10	67 ± 8	0.20

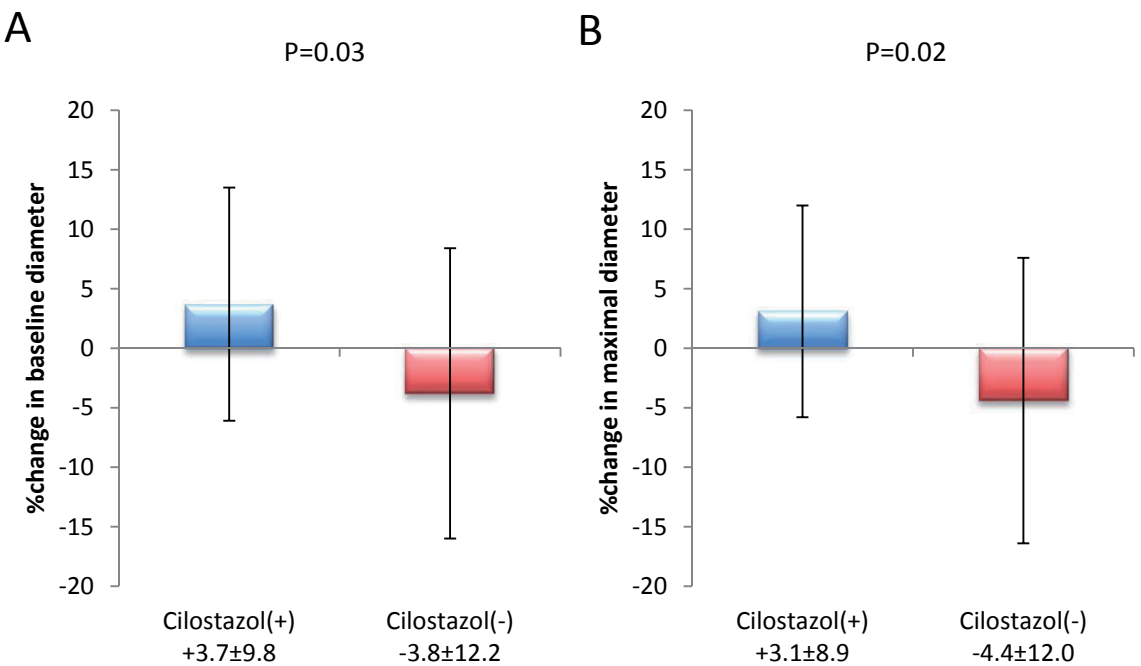

Fig. 2. The percent change in baseline and maximal brachial artery diameter

the Cilostazol(−) group (baseline: 4.1 ± 0.6 to 3.9 ± 0.5, P = 0.10; maximal: 4.3 ± 0.7 to 4.1 ± 0.5, P = 0.05). There were statistically significant differences in the percent change (**Fig. 2**) in the baseline diameter (Cilostazol(+): + 3.7 ± 9.8% vs. Cilostazol(−): − 3.8 ± 12.2%) and in the maximal diameter (Cilostazol(+): + 3.1 ± 8.9% vs. Cilostazol(−): − 4.4 ± 12.0%). The trends in blood pressure and heart rate were similar in both groups.

Discussion

To the best of our knowledge, this is the first study to investigate the effect of cilostazol on endothelial function as assessed by FMD in patients with coronary artery disease. We did not find cilostazol to affect FMD. However, there was a greater rate of change in the baseline and maximal brachial artery diameters in the Cilostazol(+) group between enrollment and follow-up in comparison to the Cilostazol(−) group. This dilation of brachial artery diameter is consistent with its well-described vasodilator effect and may be of potential benefit to patients with cardiovascular disease, especially those with peripheral artery disease.

There are several previous reports (**Supplemental Table 1**) that have studied the effects of cilostazol on endothelial function as assessed by FMD; however, these reports did not involve patients with coronary artery disease and the durations of treatment were not

as long as our study[16-20]. Three reports[16-18] investigating younger smokers found that 2 weeks of cilostazol treatment resulted in FMD improvement. These studies[16-18] indicated that younger smokers are more likely to respond to cilostazol treatment. One report[19] examined patients with silent cerebral lacunar infarction and hypercholesterolemia who received a combination of probucol and cilostazol for four weeks, and found that treatment resulted in FMD improvement. Although these cases showed similar clinical characteristics, the FMD values at enrollment were much lower than those of our study and the patient's LDL cholesterol levels at enrollment were much higher (134 ± 27 mg/dl in the Probucol + Cilostazol group, 136 ± 30 mg/dl in the aspirin group) than in our study (108 ± 28 mg/dl in the Cilostazol(+) group, 102 ± 32 mg/dl in the Cilostazol(−) group). Thus, several factors existed that could be improved by more aggressive drug therapy. In one report[20] Raynaud's syndrome patients who received cilostazol for 6 weeks showed no FMD improvement. However, similar to our study, the patients showed a significant increase in brachial artery diameter.

The addition of cilostazol, on top of conventional dual antiplatelet therapy, has been reported to be beneficial for patients with coronary artery disease who require coronary stents; however, these reports mainly measure improvement by the reduction of in-stent restenosis[21, 22]. On the other hand, there are reports that show that the addition of cilostazol on top of conventional dual antiplatelet therapy did not result in better clinical outcomes in patients with coronary artery disease who required coronary stents in comparison to conventional dual antiplatelet therapy[23, 24]. Although the endpoints of these studies differed from our own, the patient demographics were quite similar. Thus, with the knowledge of these conflicting data, that cilostazol did not improve the FMD values of the patients in our study, was not entirely unexpected.

Unlike patients with coronary artery disease, patients with peripheral artery disease are more likely to benefit from cilostazol. Cilostazol has been reported to reduce not only the risk of restenosis but also the risk of amputation in patients with cardiovascular disease[25]. The vasodilatory effect of cilostazol that we observed in our study can be beneficial to such patients. However, in spite of these effects, there is not enough evidence to support that the administration of cilostazol can reduce mortality.

Cilostazol is contraindicated for patients with severe heart failure since other PDE inhibitors such as milrinone[26] and vesnarinon[27], which are used as inotropic agents for patients with severe heart failure, have been shown to be associated with a worse clinical outcome. However, in the present study, there was a significant decrease in BNP levels in the Cilostazol(+) group. This result indicates the possible utility of cilostazol in the treatment of patients with coronary artery disease but without heart failure.

Study Limitations

There are several limitations associated with this study. First, this was not a double-blind study and there was no placebo, although the endothelial functions were assessed in a blinded manner. Second, FMD is highly dependent on the baseline brachial diameter[28]; a large baseline vessel diameter is correlated with a low FMD value. As a result, the vasodilation effect of cilostazol likely affected FMD readings. Third, the study was performed at a single center with a small study population and we did not administer the maximum dose of cilostazol. However, in the present study, the addition of cilostazol did not result in any improvement in FMD. The percent change in FMD was somewhat worse in the Cilostazol(+) group but did not reach statistical significance. We are therefore of the opinion that it is very difficult to show that the addition of cilostazol results in an improvement in FMD, even if we increase the number of cases.

Conclusion

Although cilostazol did not affect FMD in patients with coronary artery disease, the increased baseline and maximal brachial artery diameter and the significant difference in the rate of change, suggests that cilostazol may be beneficial for patients with cardiovascular disease.

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Disclosures

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Supplemental Table 1. Comparisons with previous publications

Study demographic						FMD data in cilostazol group		
Author	Case characteristics	Case (*n*)	Age	Duration	Therapy	Enrollment	Follow-up	*P*-value
Mori *et al.*	Coronary artery disease	22	67 ± 7	6–9 months	Cilostazol (100 mg/day) and conventional dual antiplatelet therapy	5.2 (3.8-8.5)	5.4 (4.2-6.7)	0.29
		22	66 ± 10		Conventional dual antiplatelet therapy	5.0 (3.6-6.4)	4.9 (4.0-7.0)	0.38
Oida *et al.*	Smoker	20	38 ± 5.2	2 weeks	Cilostazol (150 mg/day)	4.2 ± 1.2	7.8 ± 3.5	0.003
Kim *et al.*	Smoker	20	29.1 ± 1.9	2 weeks	Cilostazol (200 mg/day)	8.0 ± 2.1	12.2 ± 5.1	0.003
	Non-smoker	10	28 ± 1.1			12.0 ± 4.5	16.1 ± 3.7	0.041
Jeong *et al.*	Smoker	20 (cross over with 1 week interval)	29 ± 2	2 weeks	Cilostazol (200 mg/day)	7.7 ± 1.9	8.8 ± 2.0	0.016
					Sarpogrelate (200 mg/day)	7.4 ± 1.9	8.8 ± 1.9	0.021
Takae *et al.*	Silent cerebral Lacunar infarcts and hypercholesterolemia	17	72 ± 7	4 weeks	Cilostazol (200 mg/day) and Probucol (500 mg/day)	2.69 ± 1.51	3.53 ± 1.69	< 0.05
		17	72 ± 8		Aspirin (100 mg/day)	2.63 ± 1.48	2.92 ± 1.39	NS
Rajagopalan *et al.*	Raynaud's syndrome (primary)	19	47 ± 12	6 weeks	Cilostazol (200 mg/day)	4.06 (2.5-6.1)	− 0.77 (− 2.4-3.5)	NS
					Placebo	Not available		
	Raynaud's syndrome (secondary)	20	41 ± 13		Cilostazol (200 mg/day)	2.23 (0.05-6.3)	2.95 (1.7-7.4)	NS
					Placebo	Not available		

FMD = flow-mediated dilation.