Effect of the Novel Antiplatelet Agent Cilostazol on Plasma Lipoproteins in Patients With Intermittent Claudication

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Abstract—Cilostazol is an antiplatelet agent and vasodilator marketed in Japan for treatment of ischemic symptoms of peripheral vascular disease. It is currently being evaluated in the United States for treatment of symptomatic intermittent claudication (IC). Cilostazol has been shown to improve walking distance in patients with IC. In addition to its reported vasodilator and antiplatelet effects, cilostazol has been proposed to have beneficial effects on plasma lipoproteins. We examined the effect of cilostazol versus placebo on plasma lipoproteins in 189 patients with IC. After 12 weeks of therapy with 100 mg cilostazol BID, plasma triglycerides decreased 15% ($P<0.001$). Cilostazol also increased plasma high density lipoprotein cholesterol (HDL-C) (10%) and apolipoprotein (apo) A1 (5.7%) significantly ($P<0.001$ and $P<0.01$, respectively). Both HDL_3 and HDL_2 subfractions were increased by cilostazol; however, the greatest percentage increase was observed in HDL_2. Individuals with baseline hypertriglyceridemia (>140 mg/dL) experienced the greatest changes in both HDL-C and triglycerides with cilostazol treatment. In that subset of patients, HDL-C was increased 12.2% and triglycerides were decreased 23%. With cilostazol, there was a trend (3%) toward decreased apoB as well as increased apoA1, resulting in a significant (9.8%, $P<0.002$) increase in the apoA1 to apoB ratio. Low density lipoprotein cholesterol and lipoprotein(a) concentrations were unaffected. Cilostazol treatment resulted in a 35% increase in treadmill walking time ($P=0.0015$) and a 9.03% increase in ankle-brachial index ($P<0.001$). These results indicate that in addition to improving the symptoms of IC, cilostazol also favorably modifies plasma lipoproteins in patients with peripheral arterial disease. The mechanism of this effect is currently unknown. **(*Arterioscler Thromb Vasc Biol*. 1998;18:1942-1947.)**

Key Words: HDL ■ intermittent claudication ■ triglycerides ■ cilostazol ■ apoA1

Cilostazol is a vasodilator and platelet aggregation inhibitor that has been marketed since 1988 in Japan for treatment of ischemic symptoms of peripheral vascular disease. Cilostazol {6[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2-(1*H*)-quinolinone} is a 2-oxoquinolone derivative (molecular weight, 369.47) that has a plasma half-life of 10.5±4.4 hours after oral administration (Figure 1). Cilostazol inhibits both primary and secondary platelet aggregation in response to ADP, collagen, epinephrine, and arachidonic acid.[1,2] The antiplatelet and vasodilator properties of cilostazol have been attributed to its ability to elevate intracellular levels of cAMP.[3] Cilostazol is currently being evaluated in the United States for treatment of symptomatic intermittent claudication (IC). Japanese studies performed in diabetic patients have indicated that, in addition to its vasodilator and antiplatelet properties, cilostazol may also favorably modify plasma lipoproteins by increasing HDL cholesterol (HDL-C) and reducing triglycerides.[4] The purpose of the present study was to determine whether cilostazol favorably modifies plasma lipoproteins in a general population of patients with stable IC.

Methods

Patient Population

The study included subjects with documented chronic, stable, symptomatic IC secondary to peripheral arterial disease (PAD). PAD was defined as an ankle-brachial index (ABI) ≤0.90; termination of walking on a variable-load, constant-speed treadmill due to IC (>54 and <805 m); and a Doppler-measured drop of ≥10 mm Hg in blood pressure of 1 ankle after the treadmill test. For patients without a qualifying ABI, a 20–mm Hg drop in postexercise ankle artery pressure was required for entry. Patients with documented IC underwent 2 fasting blood draws (at least 1 week apart) in which plasma triglyceride concentration (average of 2 determinations) was <350 mg/dL, and plasma LDL-C was between 100 and 190 mg/dL in all subjects.

Subjects were men and women >40 years of age. Women were not of child-bearing potential (they either had been surgically sterilized or were at least 1 year postmenopausal). Subjects with

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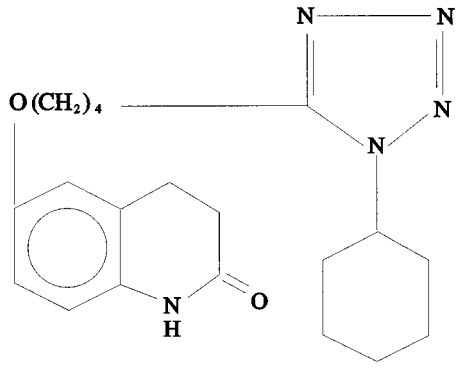

Figure 1. Chemical structure of cilostazol {6[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2-(1*H*)-quinolinone}. Cilostazol is an inhibitor of type III (cyclic GMP–inhibited) phosphodiesterase and has antiplatelet and vasodilator properties.

gross obesity (>60% above ideal body weight), poorly controlled hypertension (systolic pressure >200 mm Hg; diastolic pressure >100 mm Hg), poorly controlled diabetes, a history of malignancy, current alcohol or drug abuse, renal disease (creatinine >2.5 mg/dL), or bleeding tendencies were excluded. Antiplatelet, anticoagulant, vasoactive, hemorheologic, or lipid-modifying medications were not allowed during the 12-week-study treatment period. Therapy with β-blockers and thiazide diuretics was allowed if held at a constant dose for 8 weeks before the trial and if the dosage was maintained during the 12-week treatment period. All study participants discontinued lipid-lowering therapy at least 4 weeks before screening, with the exception of probucol, which was to be discontinued 6 months before screening. Enrollees were instructed to maintain stable dietary patterns during the 12-week study period.

Study Design

This study was a multicenter, randomized, parallel, double-blind trial with the administration of either cilostazol, 100 mg PO, BID, or placebo PO, BID, for a period of 12 weeks. Study participants were evaluated at study weeks 2, 4, 6, 8, and 12. Standardized treadmill walking tests were conducted at 2 baseline visits and weeks 8 and 12. The primary outcome variables from lipid profiling were as follows: total cholesterol, LDL, HDL-C (total HDL-C, HDL_2, and HDL_3), lipoprotein$_a$ (Lp_a, when ≥30 mg/dL), apoA1, apoB, and triglycerides. All lipid analyses were blinded to the investigators and patients after randomization. The primary outcome variables for exercise tolerance were pain-free walking distance and maximal walking distance. Pain-free walking distance was defined as the distance walked before initial onset of pain. Maximal walking distance was defined as the maximum distance walked.

Lipid Assays

Plasma cholesterol, triglycerides, HDL-C, and LDL-C were determined by the central laboratory at Bowman Gray School of Medicine (Winston-Salem, NC). Blood for analysis of plasma concentrations of lipids and lipoproteins was obtained from fasting participants (12 hours without food, 24 hours without alcohol). Plasma was immediately isolated by low-speed centrifugation. Samples were shipped on wet ice to the Bowman Gray Lipid Analytic Laboratory and analyzed using methods standardized by the Centers for Disease Control and Prevention, Atlanta, Ga. Cholesterol and triglyceride analyses were performed on whole plasma with and without heparin-$MnCl_2$ precipitation using a Technicon RA 1000 Auto-analyzer.[5] HDL-C was determined by the heparin-manganese precipitation method, first reported by Burstein and Samaille.[6] HDL_2/HDL_3 subtypes were analyzed using the dextran sulfate precipitation method of Gidez et al.[7] LDL was calculated using the method of Friedewald et al.[8] ApoA1 and apoB were measured on human plasma immunoturbidimetrically using a Cobas Fara II centrifugal analyzer and antibodies against human apoA1 and apoB provided by Sigma Chemical Co (for apoA1, Sigma procedure 356; for apoB, Sigma procedure 357). Lp_a was measured on human plasma by automated immunoprecipitin analysis using a Cobas Fara II centrifugal analyzer and antibodies against human Lp_a provided by INCSTAR Corp (catalog No. 86084).

Statistical Analysis

Continuous efficacy measures were analyzed by ANOVA and the Wilcoxon rank sum test. The former method was used when the residuals for the response variables were normally distributed; otherwise, the Wilcoxon rank sum test was used. Sample size was based on determination of a clinically meaningful difference in HDL between groups (4 mg/dL). The minimum sample size chosen (n=75) provided >80% power based on a 5% significance level (2-sided). The primary analysis for lipids was the change from baseline to the last observation. Secondary analyses of the effect of pretreatment HDL and triglycerides and of β-blocker and diuretic therapy on the lipoprotein response to cilostazol were conducted to provide additional information regarding the potential mechanism of the lipid effect. The protocol was approved by the Institutional Review Board at each study center. Written, informed consent was obtained from each patient before entry into the study.

Results

One hundred eighty-nine study participants were randomized to receive therapy with either cilostazol (n=95) or placebo (n=94). The 2 treatment groups were similar with regard to demographics, PAD severity, concurrent illnesses, concurrent medications, and baseline lipoproteins, with the following exceptions: Significantly more patients randomized to placebo reported prior coronary artery bypass grafting and diuretic therapy, and baseline levels of total cholesterol, apoA1, and apoB were higher in the placebo group (Table 1). As expected in a population of claudicants, there was a high prevalence of comorbid disease including hypertension, coronary heart disease, and diabetes mellitus. Although the cohort was predominantly white and male, significant numbers of female (n=30) and minority (n=28) participants were included as well. Of the 189 patients who were randomized, 170 (89.9%) completed the study (ie, had a week-12 visit). The number of patients who completed the study was comparable between the treatment groups: 86.3% cilostazol (n=82) and 93.6% placebo (n=88).

The most commonly reported adverse effects reported by study participants during the 12-week study period were headache, diarrhea, musculoskeletal pain, abnormal stools, dizziness, and peripheral edema (Table 2). Significantly more participants in the cilostazol treatment group reported headache compared with placebo. In most cases these symptoms were transient, responded to symptomatic treatment, and did not require discontinuation of treatment. Four patients discontinued cilostazol treatment because of persistent headache, and 1 patient discontinued cilostazol therapy due to diarrhea. No increases 2-fold or greater in liver transaminases were seen in either treatment group.

Effect of Cilostazol Treatment on Plasma Lipoproteins

After 12 weeks of treatment with cilostazol, there was a significant decrease (15%) in plasma triglycerides and an increase (9.5%) in plasma HDL-C compared with placebo (Figure 2). These lipoprotein effects were observed after 2 and 4 weeks of cilostazol treatment for HDL-C and triglycerides, respectively, and continued throughout the remaining 8 weeks of treatment. By comparison, plasma HDL-C and triglycerides remained stable during the 12-week treatment period in the placebo group. LDL-C levels were not signifi-

TABLE 1. Patient Characteristics by Treatment

	Cilostazol	Placebo
n	95	94
Age, y	66.7	65.8
Sex		
Male	83 (87.4%)	76 (80.9%)
Female	12 (12.6%)	18 (19.1%)
Race		
White	84 (88.4%)	77 (81.9%)
Minority	11 (11.6%)	17 (18.1%)
Weight, kg	81.7	81.1
Baseline ABI, affected limb	0.66	0.65
Baseline PFD, m	122.2	142.3
Baseline MWD, m	262.3	278.2
Plasma creatine, mg/dL	1.30±0.09	1.16±0.03
Concurrent illness		
Hypertension	53 (55.8%)	57 (60.6%)
Prior myocardial infarction	10 (10.6%)	16 (17.1%)
Angina pectoris	8 (8.4%)	10 (10.6%)
Diabetes	18 (18.9%)	19 (20.2%)
Concurrent medications		
β-Blocker	13 (13.7%)	16 (17.0%)
Diuretic	21 (22.1%)	30 (31.9%)
Oral hypoglycemic	9 (9.5%)	12 (12.8%)
Insulin	6 (6.3%)	8 (8.5%)
Plasma lipoproteins, mmol/L		
Cholesterol	5.46±0.08	5.67±0.08
Triglycerides	1.75±0.79	1.88±0.09
HDL-C	1.08±0.03	1.15±0.03
HDL_2	0.12±0.01	0.14±0.01
HDL_3	0.96±0.03	1.01±0.02
LDL-C	3.54±0.05	3.67±0.05
ApoA1, mg/dL	127±2	136±3
ApoB, mg/dL	119±2	125±2
Lp_a, mg/dL	58±4	67±4

PFD indicates pain-free distance; MWD, maximal walking distance. Data are mean (percent) and mean±SEM for discrete and continuous variables, respectively.

cantly different with cilostazol treatment (Figure 2). In addition to significant changes in triglycerides and HDL-C, cilostazol therapy was accompanied by a significant increase in plasma apoA1 (Table 3). There was a small but significant decrease in plasma apoB, which when combined with the increased apoA1, resulted in an increase in the apoA1 to apoB ratio. The increase in HDL-C appeared to result from increases in both HDL_2 and HDL_3, although the former did not reach statistical significance. The apoB to LDL-C ratio, an index of LDL density, was unchanged by cilostazol treatment (Table 3). Plasma cholesterol, LDL-C, and Lp_a (measured in patients with baseline Lp_a >30 mg/dL) were unchanged after cilostazol treatment (Table 3). There were no significant changes in plasma lipoproteins between weeks 0 and 12 in the placebo group.

TABLE 2. Most Commonly Reported Adverse Events in Cilostazol and Placebo Treatment Groups

Symptom/Severity	Cilostazol (n=95)	Placebo (n=94)
Headache	31 (32.6%)*	12 (12.8%)
Diarrhea	18 (18.9%)	8 (8.5%)
Musculoskeletal pain	14 (14.7%)	11 (11.7%)
Abnormal stools	13 (13.7%)	7 (7.4%)
Dizziness	12 (12.6%)	4 (4.3%)
Peripheral edema	11 (11.6%)	5 (5.3%)

Presented are number and percent of study subjects experiencing adverse events by treatment group during the 12 weeks of the study. *P* values were obtained from Fisher's exact test, *$P<0.05$.

Effect of Baseline HDL-C and Triglycerides on Lipoprotein Response to Cilostazol

The population of patients studied included individuals with a wide range of HDL and triglyceride levels, including a significant number of normolipidemic subjects. To determine whether patients with low HDL-C or hypertriglyceridemia were more likely to benefit from the lipoprotein-modifying effect of cilostazol, the HDL and triglyceride response to the drug was examined after stratifying the patients by baseline HDL-C <0.94 mmol/L (<36 mg/dL) and triglycerides >1.58 mmol/L (>140 mg/dL). The HDL response to cilostazol was unaffected by baseline HDL levels. Patients with low HDL-C experienced increased HDL-C with cilostazol treatment equivalent to that of subjects with higher baseline

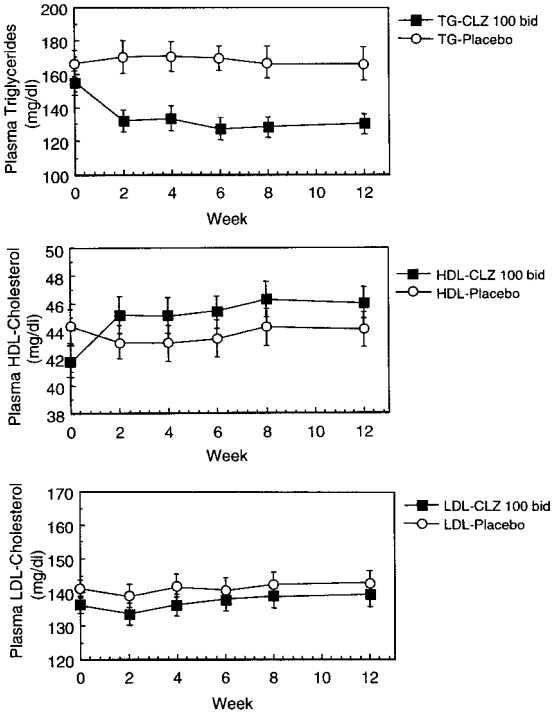

Figure 2. Time course of cilostazol effects on plasma lipoproteins. Data are mean±SEM of plasma HDL-C, LDL-C, and triglycerides at pretreatment baseline (mean of 2 determinations taken 1 week apart) and during the 12-week treatment period for subjects randomized to cilostazol (n=95) or placebo (n=94). Cilostazol treatment resulted in a significant ($P<0.001$) increase in HDL-C and decreased triglycerides by Wilcoxon rank sum test on change from baseline.

TABLE 3. Effect of Cilostazol Versus Placebo on Plasma Lipids, Lipoproteins, and Apolipoproteins

	Cilostazol (n=95)			Placebo (n=94)		
Lipoprotein Variable	Week 0	Week 12	Change	Week 0	Week 12	Change
Cholesterol, mmol/L	5.46±0.08	5.51±0.10	0.5%	5.67±0.08	5.75±0.10	+1.4%
Triglycerides, mmol/L	1.84±0.08	1.47±0.07	−15%*	1.85±0.09	1.88±0.11	+1.2%
HDL-C, mmol/L	1.09±0.03	1.20±0.03	+9.5%*	1.14±0.03	1.14±0.03	0%
HDL_2, mmol/L	0.12±0.01	0.20±0.02	+56%	0.14±0.01	0.18±0.02	+32%
HDL_3, mmol/L	0.99±0.03	1.01±0.03	+3%†	1.01±0.03	0.96±0.03	−5%
ApoA1, mg/dL	128±3	136±3	+6.3%‡	135±3	137±3	+1.5%
LDL-C, mmol/L	3.56±0.08	3.61±0.08	+1%	3.67±0.05	3.69±0.08	+0.7%
ApoB, mg/dL	119±2	116±2	−2.5%†	124±2	126±2	+1.6%
ApoA1/apoB	1.10±0.03	1.19±0.03	+8%*	1.10±0.03	1.11±0.03	+0.9%
ApoB/LDL-C	0.88±0.01	0.85±0.01	−3%	0.89±0.01	0.89±0.01	0%
Lp_a§	58±4	56±5	−3.4%	67±4	65±4	−0.3%

Data are mean±SEM for cilostazol and placebo treatment groups, respectively. Significance of differences in week-12 versus week-0 plasma lipoproteins between groups were tested by Wilcoxon rank sum test on change from baseline: ‡$P<0.05$, †$P<0.01$, *$P<0.001$.

§Subjects with $Lp_a>30$ mg/dL (n=47) only.

HDL-C. In contrast, plasma triglyceride was decreased and HDL-C increased to a greater extent in patients whose baseline triglyceride was elevated (Table 4).

Correlation of Change in Physical Activity and Glycemic Measures With Lipoprotein Response to Cilostazol

To determine whether the observed changes in plasma HDL-C and triglycerides might have been the result of increased exercise level or improved glycemic control in cilostazol-treated patients rather than a direct hypolipidemic effect of the drug, the observed changes in HDL-C and triglycerides were correlated with indices of IC and glycemic control across all patients (Table 5). Both treadmill distance (maximal) and ABI improved significantly ($P=0.004$ and $P<0.001$, respectively, versus placebo) in cilostazol-treated patients compared with placebo-treated patients; however, there was no significant correlation of change in either maximal walking distance or ABI with change in the lipoprotein variables. Neither fasting glucose nor glycosylated hemoglobin was influenced by cilostazol treatment. Moreover, cilostazol had little effect on glycosylated hemoglobin regardless of diabetic status. There was no correlation of either of these variables with change in the lipoprotein variables. Finally, to determine whether the observed increase in HDL-C after cilostazol treatment was related to decreased triglycerides, we examined the relationship of the change in triglycerides with the change in HDL-C. Surprisingly, there was no significant correlation between change in triglycerides and in HDL-C.

Effect of β-Blocker and Diuretic Therapy on Lipoprotein Response to Cilostazol

Both β-blockers and diuretics are known to modify plasma triglycerides and HDL-C. Because of the prevalence of concomitant hypertension and coronary heart disease among study participants, many patients were being treated with these agents and this was allowed, provided the dose was held constant during the 12-week treatment period. On the other hand, it is possible that these agents might have prevented or blunted the effect of cilostazol on plasma lipoproteins. In particular, if cilostazol exerted its lipoprotein-modifying effects by increasing intracellular cAMP as a result of its ability to inhibit phosphodiesterase, that response might be altered

TABLE 4. Effect of Pretreatment HDL-C and Triglycerides on Lipoprotein Response to Cilostazol

		HDL-C			Triglycerides		
	n	Week 0 Mean±SEM	Week 12 Mean±SEM	Change	Week 0 Mean±SEM	Week 12 Mean±SEM	Change
Pretreatment HDL-C							
<0.94 mmol/L	29	0.84±0.01	0.95±0.01	+13.7%	2.07±0.15	1.61±0.13	−22.0%
≥0.94 mmol/L	57	1.24±0.04	1.35±0.04	+9.0%	1.60±0.08	1.36±0.08	−15.0%
Pretreatment triglycerides							
≤1.58 mmol/L	37	1.15±0.05	1.24±0.05	+7.7%	1.19±0.04	1.12±0.06	−6.6%
>1.58 mmol/L	43	1.05±0.04	1.18±0.05	+12.2%*	2.26±0.09	1.74±0.10	−23%*

Data are mean±SEM of plasma HDL-C and triglycerides at baseline (week 0) and after 12 weeks of cilostazol therapy stratified by baseline HDL-C and triglycerides.

*$P<0.05$ for difference in lipoprotein response to cilostazol by pretreatment lipoprotein by ANOVA. Subjects were divided into those with pretreatment HDL-C ≥ or <36 mg/dL and triglycerides ≥ or <140 mg/dL.

TABLE 5. Change in Exercise Capacity, ABI, Glycemic State, or Lipoprotein Does Not Predict Change in Plasma HDL-C or Triglycerides With Cilostazol Treatment

	Change in Patient Variables		Correlation With Change in	
Variable	Baseline	Week 12	HDL-C	Triglycerides
MWD, m				
Cilostazol	262±17	335±24 (35.5%)	0.009	0.048
Placebo	278±17	304±23 (24.3%)		
ABI				
Cilostazol	0.66±0.02	0.73±0.02 (9.03%)	−0.054	−0.075
Placebo	0.65±0.02	0.65±0.02 (1.2%)		
Fasting blood glucose				
Cilostazol	6.31±0.22	6.53±0.22 (3.2%)	−0.099	0.028
Placebo	6.15±0.22	6.15±0.22 (−0.3%)		
HbA1c				
Cilostazol	4.87±0.08	4.87±0.10 (0%)	0.02691	−0.030
Placebo	4.70±0.08	4.74±0.09 (0.8%)		
HDL-C				
Cilostazol	1.09±0.03	1.20±0.03 (11.5%)	...	−0.160
Placebo	1.14±0.03	1.14±0.03 (1.1%)		
Triglycerides				
Cilostazol	1.75±0.08	1.44±0.08 (−14.4%)	−0.160	...
Placebo	1.85±0.09	1.88±0.11 (1.8%)		

MWD indicates maximal walking distance; HbA1c, glycosylated hemoglobin. Data are mean±SEM of subject variables at baseline (week 0) and after 12 weeks of cilostazol therapy, with Pearson *R* values for correlation of change in lipid variables with change in tested variables. Values in parentheses are mean percent change from baseline to week 12.

by blockade of β-receptors. Analysis of the HDL-C and triglyceride response to cilostazol in subjects being treated with diuretics or β-blockers showed no effect of either agent on the lipoprotein response to cilostazol, with the exception of patients on diuretic therapy, who had a reduced triglyceride-lowering effect compared with those not on diuretic therapy (−6% versus −16%). This may reflect antagonism of cilostazol's triglyceride-lowering effect by diuretic therapy. Alternatively, the reduced triglyceride response in the group of study participants on diuretic therapy may merely reflect the lower baseline triglyceride values in that group. Individuals with low baseline triglycerides had a lower decrease of triglycerides with cilostazol, as discussed earlier. The absence of an effect of β-antagonist therapy on lipoprotein response to cilostazol does not eliminate the possibility that increased intracellular cAMP levels may mediate the lipoprotein effects of cilostazol, but it argues against a requirement for β-adrenoceptor–mediated increases in cAMP.

Discussion

This study demonstrates that, in addition to its vasodilator and antiplatelet properties, the phosphodiesterase inhibitor cilostazol also favorably modifies plasma lipoproteins. Specifically, plasma levels of HDL-C and apoA1 are significantly increased and plasma triglycerides are decreased. Both the triglyceride-lowering and HDL-raising effects of cilostazol are more pronounced in individuals with baseline hypertriglyceridemia. The only previous report of the lipid-modifying effect of cilostazol is a study of a limited number of diabetic subjects in the Japanese literature.[4] This prior study reported effects of cilostazol on plasma lipoproteins, which were comparable to those reported here.

Current treatment guidelines recommend aggressive cholesterol lowering and risk-factor modification in individuals with known coronary heart disease and other symptomatic vascular disease, including PAD.[9] Individuals with PAD are at high risk of death and disability from coronary and cerebrovascular disease, in addition to the morbidity associated with PAD itself. The risk of fatal cardiovascular events in subjects with PAD is increased from 2- to 15-fold, depending on the severity of the underlying PAD.[10–12] Therefore, patients with IC have great potential to benefit from lipoprotein modification, not only to alter the clinical course of PAD itself, but also to modify coexisting atherosclerotic vascular disease. The ability of cilostazol to favorably modify plasma triglycerides and HDL-C is particularly significant for patients with IC, in that both hypertriglyceridemia and low HDL-C are observed with increased frequency in such patients.[13–17] Reduced plasma triglycerides may be desirable in this patient population, as elevated plasma triglyceride levels are associated with increased risk of cardiovascular disease independent of HDL-C.[18,19]

The exact mechanisms involved in the ability of cilostazol to lower plasma triglycerides and increase HDL are at present unknown. The lipoprotein effects of cilostazol that we have observed appear to be independent of changes in physical activity or glucose tolerance and are unaffected by concomitant β-antagonist therapy. It is likely that the lipoprotein effects of cilostazol are a result of its ability to inhibit cyclic nucleotide phosphodiesterase and thereby elevate intracellular cAMP. Cy-

clic nucleotide phosphodiesterases regulate intracellular levels of cAMP (and cGMP) by catalyzing their degradation.[20] There are several possible mechanisms by which increased cAMP might result in lowered plasma triglycerides. One possible mechanism is by reducing hepatic triglyceride (ie, VLDL) secretion, either directly, or indirectly by potentiating the effect of glucagon to inhibit VLDL secretion.[21] On the other hand, increased cAMP levels have been shown to promote release of lipoprotein lipase from rat adipocytes,[22] which could reduce plasma triglycerides. Although plasma lipoprotein lipase was not measured as part of the present study, increased plasma lipoprotein lipase has been observed in streptozotocin diabetic rats treated with cilostazol (Otsuka America Pharmaceutical, unpublished data, 1994).

In the present study, the time course of the effect of cilostazol on HDL-C differed from that of its effect on triglycerides. In addition, the change in HDL-C was not correlated with the decrease in triglycerides during cilostazol treatment. This suggests that different mechanisms may be responsible for the effect of cilostazol on triglycerides and HDL. In this regard, there are no published studies of the effect of cAMP on expression of apoA1 by the liver or gut. On the other hand, the previous observation that increased cAMP levels enhance HDL_3-mediated sterol efflux from cholesterol-loaded human skin fibroblasts[23] indicates 1 possible mechanism for increased HDL-C after phosphodiesterase inhibitor treatment.

The observed beneficial lipoprotein-modifying effect of cilostazol, in addition to its previously reported antiplatelet properties, offers the possibility that long-term therapy with this agent will not only alleviate the symptoms of IC but may also favorably alter the clinical course of atherosclerotic peripheral vascular disease. This remains to be determined and will require long-term study of the effects of cilostazol.

Appendix: Treatment Centers and Study Investigators

H. Beebe, MD, Jobst Vascular Center, Toledo, Ohio; Lt Col D.L. Dawson, MD, Wilford Hall USAF Medical Center, San Antonio, Tex; L.K. Smith, MD, Arizona Heart Institute, Phoenix, Ariz; S.E. Wilson, MD, University of California at Irvine, Orange, Calif; R. Hobson, MD, UMDNJ, Newark, NJ; I. Gordon, MD, VA Medical Center, Long Beach, Calif; J.R. Crouse, MD, Bowman Gray Medical Center, Winston-Salem, NC; J.A. Herd, MD, The Methodist Hospital, Houston, Tex; D.B. Hunninghake, MD, University of Minnesota, Minneapolis; M.B. Elam, MD, PhD, VAMC/University of Tennessee, Memphis; A.B. Alvaro, MD, California Clinical Trials Medical Group, Beverly Hills, Calif; J. Regensteiner, PhD, University of Colorado Health Sciences Center, Denver, Colo; M. Davidson, MD, Chicago Center for Clinical Research, Chicago, Ill; E. Dyckman, MD, CRF Inc, Atlanta, Ga; M. Rendell, MD, Creighton Diabetes Center, Omaha, Neb; R. Ratner, MD, Washington Center Hospital, Washington, DC; P. Comp, MD, PhD, Oklahoma Memorial Hospital, Oklahoma City, Okla.

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