Effect of Cilostazol in Patients with Intermittent Claudication: A Randomized, Double-Blind, Placebo-Controlled Study

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A multicenter, double-blind, randomized, placebo-controlled, parallel study was conducted to compare the efficacy and safety of cilostazol 100 mg and 50 mg, both administered twice daily, with that of placebo in patients with moderately severe intermittent claudication (IC) secondary to peripheral arterial disease. A total of 394 subjects 40 years of age or older with chronic, stable, symptomatic IC received cilostazol 100 mg twice daily, 50 mg twice daily, or placebo for 24 weeks. Subjects receiving cilostazol 100 mg twice daily experienced a 21% net improvement in maximal walking distance (MWD) compared with placebo subjects ($p = 0.0003$) and a 22% net improvement in distance walked to the onset of symptoms (PFWD) ($p = 0.0015$). Subjects who received cilostazol 50 mg twice daily also benefited from therapy, but not to a statistically significant degree (7% and 11% improvement in MWD and PFWD, respectively). Quality-of-life and functional status assessments corroborated these objective results. Cilostazol, in particular 100 mg twice daily, significantly improves symptoms in patients with IC.

Introduction

Intermittent claudication (IC), characterized by pain, aching, cramping, or muscle fatigue of the affected extremity during exercise, is the first recognizable symptom of peripheral arterial disease (PAD).[1] Approximately 5% of men and 2.5% of women 60 years of age or older have IC.[2,3] However, these data appear to be an underestimation of the true prevalence of the disease, because IC is diagnosed in at least three times as many individuals when sensitive noninvasive tests are used.[4] Importantly, the incidence of IC increases with age; thus, the prevalence can be expected to increase with the so-called graying of America. Eventually, 7% of patients with IC re-

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quire bypass surgery; less than 4% undergo amputation.[5] Data from the Framingham study indicate that 75% of patients with IC will die of a coronary or cerebrovascular event, reflecting the risk associated with widespread arterial disease in these patients.[6]

Treatment options for IC include behavioral modification to reduce risk factors, medical therapy, and revascularization.[7] Until 1999, only one pharmacologic agent, pentoxifylline, was available for the medical treatment of IC, and the value of this agent has been limited by its variable efficacy in clinical practice. We report the results of a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel study evaluating cilostazol, a type III phosphodiesterase inhibitor. The objective of our study was to compare the efficacy and safety of twice-daily cilostazol 100 mg or 50 mg with placebo in patients with moderate IC secondary to PAD.

Methods

Study Design and Entry Criteria

Subjects enrolled in the multicenter, randomized, double-blind, 24-week, placebo-controlled parallel-design trial were randomly assigned to one of three treatment groups: cilostazol 100 mg twice daily, cilostazol 50 mg twice daily, or placebo twice daily. Eligible patients were 40 years of age or older who had at least a 6-month history of stable, symptomatic IC secondary to PAD, reproducible walking distances on screening treadmill tests, and termination of all screening treadmill tests solely for reasons of claudication pain. Stable disease was defined as 20% or less variance in maximal walking distance (MWD) on two consecutive treadmill tests. Subjects were required to walk between 30 and 200 m to be eligible. The symptom-limiting leg, termed the reference leg, was required to remain the same during the screening phase. For subjects with equivalent bilateral disease, the limb with the lowest resting ankle–brachial index (ABI) was chosen as the reference leg. Treadmill testing was performed uniformly at all sites with a standardized 2 mph, 12.5% grade protocol. Additionally, subjects were required to have a resting ABI less than 0.90 and at least a 10-mm Hg decrease in ankle systolic blood pressure in the reference leg at the completion of testing.

Exclusion criteria included ischemic pain at rest, gross obesity, childbearing potential in women, hypertension (> 200 mm Hg systolic or > 100 mm Hg diastolic supine resting pressures), malignancy or metastatic malignancy, exercise-limiting cardiac disease, history of bleeding tendencies, and concomitant use of antiplatelet, anticoagulant, hemorheologic, or nonsteroidal anti-inflammatory agents. Occasional use of diclofenac sodium was allowed. Before undergoing screening procedures, subjects signed an informed consent form approved by the institutional review board at each participating center.

Treatment Protocol

Subjects were screened for eligibility during a 3-week run-in period. Those who were successfully randomized underwent examination biweekly for the first month and monthly thereafter. The primary efficacy endpoint was MWD, defined as the total distance walked from beginning treadmill walking until the subject could walk no further. Secondary efficacy endpoints included pain-free walking distance (PFWD), defined as total distance walked until onset of pain; Doppler-measured bilateral peripheral limb pressures assessed before exercise and at 1, 5, and 9 minutes after exercise; quality of life and functional status, as evaluated by questionnaires; end-of-treatment global therapeutic benefit as determined by physicians and subjects; cardiovascular morbidity; and all-cause mortality. An independent committee, blinded to treatment assignment, adjudicated all patient deaths and any possible cardiovascular morbid events according to the predefined morbidity criteria.

The safety evaluation included incidence of adverse events, serious adverse events, discontinuation of therapy due to adverse events, and deaths. Results of physical assessments, including physical examination, body weight, vital signs, clinical laboratory testing, and electrocardiograms (ECG), were also included in the evaluation. Adverse events, elicited by querying the subjects, were recorded and assessed for potential drug causality.

Functional status questionnaires, including the medical outcomes scale short form-36, a generalized measure of quality of life, and two disease-specific questionnaires, the walking impairment questionnaire (WIQ) and the claudication outcome measures, were administered by a centralized telephone interview.

Statistical Methods

To reduce the impact of extreme variability in walking distances, log transformation of the data was used (log [distance/ baseline]), as prespecified in the study protocol. The study was powered at 90%, based on a 5% significance level (two-sided). Treatment differences were assessed in the efficacy intent-to-treat population as the estimated treatment effect of cilostazol 100 mg twice daily versus placebo and of cilostazol 50 mg twice daily versus placebo. The primary analysis used the last observation carried forward (LOCF) approach to adjust for missing data using analysis of variance of the log (distance at week 24/baseline). No per-protocol analysis was performed. Secondary analyses were performed with last-visit and time-point analyses using LOCF, completers (ie, subjects who completed all treadmill visits), and categorical analysis. Supplementary analyses were performed using observed cases (ie, no adjustment for missing data) and raw data (ie, mean [m], change [m], and percent change from baseline). Continuous efficacy measures were determined by analysis of variance and the Wilcoxon rank-sum test. Categorical efficacy measures were analyzed by the van Elteran test and the Cochran-Mantel-Haenszel test. For the randomized intent-to-treat population, changes in safety variables from baseline were summarized using descriptive statistics and shift tables, as appropriate. The cumulative probability of cardiovascular morbidity/all-cause mortality events was assessed by the Kaplan-Meier product limit estimator.

Results

A total of 557 patients from 34 centers across the United States were initially enrolled in the study, 394 of whom met study criteria and were randomly assigned to one of the three treatment groups: cilostazol 100 mg twice daily (n = 133), cilostazol 50 mg twice daily (n = 132), or placebo (n = 129) (Figure 1). There were no clinically or statistically significant differences events, serious adverse events, discontinuation of therapy due to adverse events, and deaths. Results of physical assessments, including physical examination, body weight, vital signs, clinical laboratory testing, and ECG, were also included in the evaluation. Adverse events, elicited by querying the subjects, were recorded and assessed for potential drug causality.

Functional status questionnaires, including the medical outcomes scale short form-36, a generalized measure of quality of life, and two disease-specific questionnaires, the WIQ and the claudication outcome measures, were administered by a centralized telephone interview among the treatment groups in baseline characteristics (Table I). The majority of participants (86.3%)

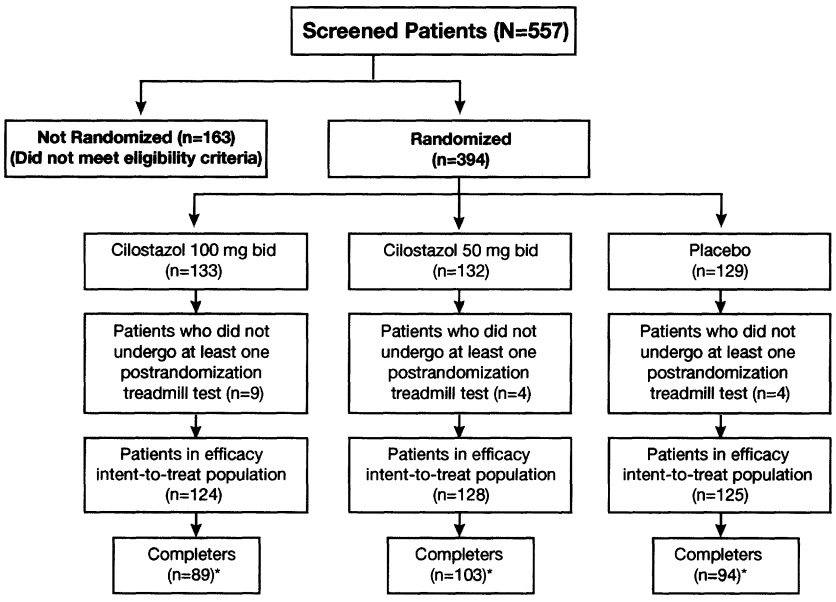

Figure 1. Patient disposition. *Completers were defined as those patients who completed all treadmill visits.

Table I. Demographics of all randomized patients.

Parameter	Cilostazol 100 mg (bid) (n = 133)	Cilostazol 50 mg (bid) (n = 132)	Placebo (n = 129)
Age (y)			
Mean ±SE	63.1 ±10.2	63.9 ±8.7	64.4 ±10.2
Range	40.0–85.0	42.0–86.0	40.0–84.0
Age category, n (%)			
< 65 y	68 (51.1)	68 (51.5)	61 (47.3)
≥ 65 y	65 (48.9)	64 (48.5)	68 (52.7)
Sex, n (%)			
Male	102 (76.7)	98 (74.2)	100 (77.5)
Female	31 (23.70)	34 (25.8)	29 (22.5)
Race, n (%)			
White	120 (90.2)	105 (79.5)	115 (89.1)
Black	12 (9.0)	21 (15.9)	11 (8.5)
Hispanic	0 (0)	4 (3.0)	2 (1.6)
Asian	0 (0)	1 (0.8)	1 (0.8)
Other	1 (0.8)	1 (0.8)	0 (0)
Weight (kg)			
N	132	130	127
Mean ± SE	80.1 ±14.8	79.6 ±14.9	80.1 ±15.1
Range	48.0–118.0	46.0–119.0	51.0–149.0
Height (cm)			
N	132	130	170
Mean ± SE	172.3 ±8.6	171.3 ±9.6	172.2 ±8.2
Range	150.0–188.0	147.0–194.0	152.0–191.0
Diabetes, n (%)			
Yes	31 (23.3)	38 (28.8)	22 (17.1)
No	102 (76.7)	94 (71.2)	107 (82.9)
Cigarettes, n (%)			
Never	4 (3.0)	14 (10.6)	13 (10.1)
Previous	62 (46.6)	55 (41.7)	54 (41.9)
Current	67 (50.4)	63 (47.7)	62 (48.1)
Pack-Years*			
N	128	118	116
Mean ± SE	52.1 ±31.9	48.1 ±28.1	53.1 ±31.5
Range	0.5–153.0	1.0–138.0	2.5–174.0
Other tobacco products, n (%)			
Never	127 (95.5)	121 (91.7)	120 (93.0)
Previous	5 (3.8)	6 (4.5)	3 (2.3)
Current	1 (0.8)	5 (3.8)	6 (4.7)
Alcohol, n (%)			
Never	24 (18.0)	33 (25.0)	23 (17.8)
Previous	27 (20.3)	33 (25.0)	35 (27.1)
Current	82 (61.7)	66 (50.0)	71 (55.0)

were white (mean age, 63.8 years), and more than 76% were male. A total of 23% of the study population had diabetes mellitus (91 of 394); fewer diabetic subjects were assigned to the placebo group than either the 100-mg or 50-mg cilostazol groups (22, 31, and 38 subjects, respectively). The intent-to-treat population for treadmill analysis included 377 of the 394 randomized subjects (96%); 17 of the original cohort failed to complete the baseline treadmill assessment. A total of 286 subjects completed all 24 weeks of therapy and treadmill examinations.

Treadmill Data

Compared with placebo, cilostazol 100 mg produced significant improvement in MWD, beginning at week 8 and continuing throughout the study (Table II). The improvements in walking distances in subjects taking cilostazol 100 mg increased over time compared with placebo, with estimated treatment effects of 11% at week 8, 15% at week 16, and 17% at week 20, using LOCF analysis. Similar results were achieved with the completers and observed cases analyses.

Table II. Trough mean maximum walking distance and estimated treatment effect.*

Time Point	Mean MWD (m) CLZ 100 mg bid	CLZ 50 mg bid	Placebo	Treatment Comparison	Estimated Treatment Effect†	p Value‡	95% CI
Baseline	119.4 (n=133)	122.7 (n=132)	120.1 (n=128)				
Week 4	136.3 (n=120)	134.7 (n=126)	132.3 (n=122)	CLZ 100 mg bid vs placebo	1.02	0.5033	0.96–1.08
				CLZ 50 mg bid vs placebo	0.97	0.3340	0.92–1.03
				CLZ 100 mg bid vs CLZ 50 mg bid	1.05	0.1037	0.99–1.11
Week 8	160.9 (n=122)	150.4 (n=127)	135.1 (n=125)	CLZ 100 mg bid vs placebo	1.11	0.0084	1.03–1.20
				CLZ 50 mg bid vs placebo	1.03	0.4109	0.96–1.11
				CLZ 100 mg bid vs CLZ 50 mg bid	1.07	0.0671	0.99–1.16
Week 16	168.9 (n=122)	160.6 (n=127)	138.4 (n=125)	CLZ 100 mg bid vs placebo	1.15	0.0034	1.05–1.26
				CLZ 50 mg bid vs placebo	1.09	0.0738	0.99–1.19
				CLZ 100 mg bid vs CLZ 50 mg bid	1.06	0.2398	0.96–1.16
Week 20	183.9 (n=122)	168.7 (n=127)	140.0 (n=125)	CLZ 100 mg bid vs placebo	1.17	0.0035	1.05–1.29
				CLZ 50 mg bid vs placebo	1.09	0.1136	0.98–1.20
				CLZ 100 mg bid vs CLZ 50 mg bid	1.07	0.1716	0.97–1.19
Week 24	195.6 (n=124)	166.5 (n=128)	141.2 (n=125)	CLZ 100 mg bid vs placebo	1.21	0.0003	1.09–1.35
				CLZ 50 mg bid vs placebo	1.07	0.1826	0.97–1.19
				CLZ 100 mg bid vs CLZ 50 mg bid	1.13	0.0188	1.02–1.26

bid = twice daily; CI = confidence interval; CLZ = cilostazol. *Using last observation carried forward in efficacy intent-to-treat patient population (patients having = 1 postbaseline treadmill test). †Estimated treatment effect is the ratio of geometric mean (antilog of the difference in mean of cilostazol change from baseline minus mean of placebo change from baseline walking distance; this method was used because of the difficulty in obtaining 95% confidence intervals with log transformation. ‡p value on estimated treatment effect derived from analysis of variance. One patient did not receive a baseline treadmill test assessment.

The raw walking distance data for MWD (mean, mean change, and percent change from baseline) further demonstrated the marked improvement for the 100-mg cilostazol group versus placebo. The LOCF analysis at week 24 showed that walking distance increased 76.2 m from baseline in the 100 mg cilostazol group, a 63.82% improvement, compared with 20.3 m in the placebo group, a 20.8% improvement ($p = 0.0003$). The estimated treatment effect calculated for MWD in the 50 mg cilostazol group compared with the placebo group at week 24 was an improvement of 7% ($p = 0.1826$). All analyses showed a trend toward improvement in the 50 mg cilostazol group versus placebo. The raw data at week 24 demonstrated that subjects in the 50 mg cilostazol group walked 43.3 m further than at baseline, a 33.5% difference and a net improvement of 23 m compared with placebo subjects. These results show a linear dose-response relation in improvement in MWD.

Functional Status Questionnaires

Patient and physician perceptions of functional improvement paralleled objective findings. Time-point analysis of quality-of-life data revealed a trend toward greater improvement in both cilostazol groups versus the placebo group in all physical health concept scales (physical function, bodily pain, and role-physical). Furthermore, there was a statistically significant improvement in the physical function scale at week 24 for the 100 mg cilostazol group compared with placebo ($p = 0.048$). A similar positive trend was observed in the general health perception score for the cilostazol groups, as well as statistically significant differences at some time points. The improvements in the walking distance score on the WIQ also correlated with the estimated treatment effects of cilostazol.

Global Therapeutic Assessment

More subjects in the cilostazol-treated groups judged their outcomes to be better or much better relative to baseline (71/133 [53.4%] for cilostazol 100 mg twice daily; 72/132 [54.5%] for cilostazol 50 mg twice daily) than in the placebo group (51/129 [39.5%]) ($p = 0.0170$ and 0.0223 vs placebo, respectively). Similarly, more investigators judged patient outcomes to be successful in the active-treatment groups ($p = 0.0073$ for cilostazol 100 mg twice daily vs placebo; $p = 0.0061$ for cilostazol 50 mg twice daily vs placebo).

Safety

The overall incidence of adverse events rose with increasing dose, as did the overall incidence of potentially drug-related adverse events and potentially drug-related serious adverse events. The most frequently reported adverse events (occurring in at least 10% of subjects in any treatment group) were headache, infection, pain, diarrhea,

Table III. Most frequently reported treatment-emergent adverse events.*

Adverse Event	CLZ 100 mg bid (n = 133)	CLZ 50 mg bid (n = 132)	Placebo (n = 129)	Total (n = 394)
Headache, n(%)	54 (40.6)	35 (26.5)	16 (12.4)	105 (26.6)
Infection, n(%)	24 (18)	23 (17.4)	16 (12.4)	63 (16.0)
Pain,† n(%)	15 (11.3)	26 (19.7)	18 (14.0)	59 (15.0)
Diarrhea, n(%)	22 (16.5)	14 (10.6)	8 (6.2)	44 (11.2)
Abnormal stools, n(%)	26 (19.5)	8 (6.1)	7 (5.4)	41 (10.4)

CLZ = cilostazol. *At least a 10% incidence in any treatment group, regardless of relationship to study drug in the randomized intent-to-treat study population. †Refers to pain in the leg, hip, toe, thigh, or knee.

and abnormal (soft or loose) stools (Table III). Headache, diarrhea, and abnormal stools were reported more frequently in the 100 mg cilostazol group than in the 50 mg cilostazol and placebo groups. The majority of subjects in the three treatment groups (87% to 88%) rated headache as being mild or moderate in severity. Most of the headaches, regardless of treatment group, were reported within the first 2 weeks of study drug exposure.

Two subjects (both in the 100 mg cilostazol group) died within 6 months of randomization. One patient, a 70-year-old male, died of angina; another died as a result of a motor vehicle accident. Neither death was considered to be related to the study drug. Of the 394 total subjects, 67 (17%) had serious treatment-emergent adverse events: 18.8% in the 100 mg cilostazol group, 16.7% in the 50 mg cilostazol group, and 15.5% in the placebo group. The most common serious adverse event was peripheral vascular disorder, that is, worsening of claudication or peripheral vascular disease (overall incidence, 2.5%). Eleven subjects (2.8%) had serious adverse events that were considered potentially drug-related: seven (5.3%) in the cilostazol 100 mg twice daily group, three (2.3%) in the cilostazol 50 mg twice daily group, and one (0.8%) in the placebo group. Of these, seven subjects reported events that were cardiovascular in nature. Overall, 59 of 394 (15%) subjects discontinued study medication due to an adverse event: 22.6% in the 100 mg cilostazol group, 12.1% in the 50 mg cilostazol group, and 10.1% in the placebo group. Approximately twice as many subjects receiving cilostazol 100 mg twice daily discontinued the study drug as those in the placebo group, primarily due to headache (n = 6 [4.5%] vs n = 0, respectively) and cardiovascular events (n = 12 [9%] vs n = 5 [3.9%], respectively).

A life-table analysis was performed on the combined cardiovascular morbidity and all-cause mortality. Survival estimates were calculated based on the time to first occurrence of a cardiovascular event or death. Based on a log-rank test on the Kaplan-Meier estimates of survival, there were no significant differences among treatment groups (p = 0.6723) in the probability of having a cardiovascular event or dying throughout the course of the study (Figure 2).

No significant differences in other safety assessments (eg, physical examination, vital signs, and ECG) were seen among the groups. Of note, laboratory testing revealed that at all time points, subjects in the 100 mg cilostazol group had clinically significant reductions in mean triglyceride levels and increases in mean high-density lipoprotein cholesterol (HDL-C) levels. Triglycerides declined from a mean baseline of 236.2 mg/dL to a mean of 189.2 mg/dL at week 2 and to 161.6 mg/dL at week 24 ($p < 0.001$). Although subjects receiving cilostazol 50 mg twice daily also experienced statistically significant reductions in triglyceride and increases in HDL-C values, the changes were modest and not clinically significant. No other clinically relevant changes in laboratory assessments were observed.

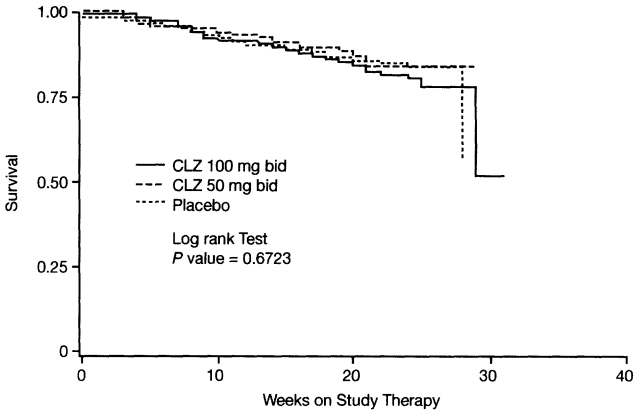

Figure 2. Kaplan-Meier estimate of cumulative probability of cardiovascular morbidity/all-cause mortality events.

Discussion

Intermittent claudication limits mobility and has a significant negative impact on quality of life in patients afflicted by the disorder. Commonly, IC patients can walk at only 1.0 mph to 2.0 mph for a distance of one-half to 4 blocks before resting.[5] Age-matched controls typically walk at 3.3 mph for unlimited distances.[7] Among persons with IC, approximately 33% report difficulty walking around their homes, and 66% indicate difficulty with walking more than 150 ft.[5]

Supervised exercise therapy is effective in increasing walking distance for IC patients who are willing and able to take part in the programs.[8,9] However, success is dependent on intensive and ongoing regimens, so patient adherence must be high. The mechanisms involved in exercise-im-

proved IC are unclear but may involve some increase in collateral blood flow and better metabolic adaptation to ischemic exercise by the affected muscle groups.

Our findings confirm those of earlier studies, showing that cilostazol consistently improves walking distance in patients with IC, as assessed both objectively and subjectively.[10-12] Money and associates reported a 47% increase in MWD at week 16 in cilostazol patients compared with a 12.9% increase in placebo patients ($p < 0.001$).[10] Patient self-assessments correlated with the objective findings. Furthermore, the ABI in the cilostazol group improved significantly compared with the placebo group (0.64 to 0.70 $\pm$0.02 and 0.68 to 0.69 $\pm$0.02, respectively; $p < 0.0125$). In a prospective, randomized, placebo-controlled, parallel-design study, Dawson and coworkers found that patients receiving cilostazol experienced a 35% increase in PFWD and 41% increase in MWD ($p < 0.01$ for both).[11] Patient and physician assessments paralleled the improvements in walking distance. Beebe and associates evaluated the safety and efficacy of cilostazol in patients with IC.[12] Compared with placebo, 100 mg cilostazol increased the geometric mean change for PFWD by 50% ($p < 0.001$); 50 mg cilostazol produced only a slightly smaller increase of 48% ($p < 0.001$).

Cilostazol has also demonstrated superiority over pentoxifylline in increasing walking distance in patients with IC.[13] In a study directly comparing the efficacy of these two agents, 698 subjects received cilostazol 100 mg twice daily, pentoxifylline 400 mg thrice daily, or placebo for 24 weeks.[13] Those in the cilostazol group showed significant improvement in PFWD and MWD compared with both pentoxifylline and placebo ($p < 0.05$). Pentoxifylline elicited no statistically significant increase in either parameter compared with placebo.

In the current study, the increase in walking distance and ABI paralleled the patient's perceived improvement as measured by both the functional status questionnaires and the global therapeutic assessment for both doses of cilostazol against placebo. This is reassuring, because it indicates that objective improvements in measured parameters were accompanied by positive patient perceptions. Although 11 subjects experienced serious adverse events that might have been drug-related, seven of which were cardiovascular in nature, the log-rank test demonstrated that there were no significant differences among the treatment groups relative to the probability of a cardiovascular event or death throughout the course of the study ($p = 0.67$).

Subjects receiving cilostazol 100 mg twice daily experienced a significant decrease in triglycerides and a clinically relevant increase in HDL-C. These effects were observed by week 2 and maintained through week 24. Another study demonstrated similar favorable effects of cilostazol on plasma lipoproteins. In 189 patients with IC treated with cilostazol 100 mg twice daily, triglyceride levels decreased 15% after 12 weeks of active therapy ($p < 0.001$ vs placebo), and HDL-C levels rose 10% ($p < 0.001$).[14] Of interest, apolipoprotein A1 levels were also decreased, while HDL–2 and HDL–3 levels were increased. Patients with hypertriglyceridemia at baseline appeared to experience the greatest benefit from cilostazol therapy. The full implications of the effects of cilostazol on lipoproteins have not yet been clarified. It is likely, however, that these favorable effects are of significance in a population at high risk for cardiovascular morbidity and mortality.

Conclusions

This study demonstrated that patients with IC who received 100 mg cilostazol twice daily experienced significant objective and subjective improvements in both PFWD and MWD compared with placebo. These effects were observed during the first weeks of therapy and were maintained throughout the study period. Cilostazol was well tolerated, with headache, diarrhea, and abnormal stools as the most frequently reported adverse events.

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