Effect of Cilostazol on Treadmill Walking, Community-Based Walking Ability, and Health-Related Quality of Life in Patients with Intermittent Claudication Due to Peripheral Arterial Disease: Meta-Analysis of Six Randomized Controlled Trials

Judith G. Regensteiner, PhD, John E. Ware, Jr, PhD,† Walter J. McCarthy, MD,‡ Peter Zhang, PhD,§ William P. Forbes, PharmD,§ Jeffrey Heckman, BS,§ and William R. Hiatt, MD**

OBJECTIVES: To assess whether cilostazol, a phosphodiesterase III inhibitor, improves treadmill and community-based walking ability and health-related quality of life (HQL) in patients with intermittent claudication resulting from peripheral arterial disease (PAD).

DESIGN: Retrospective meta-analysis of data pooled from six Phase 3, multicenter, double-blind, placebo-controlled, parallel-group, randomized studies.

SETTING: Patients were recruited from outpatient ambulatory medical care facilities.

PARTICIPANTS: Patients' (n = 1,751) mean age ± standard deviation was 65 ± 9, and they had a history of PAD for 6 months or longer and an ankle brachial index (ABI) of 0.90 or less.

INTERVENTION: Cilostazol 50 mg bid or 100 mg bid for 12, 16, or 24 weeks.

MEASUREMENTS: ABI; maximal walking distance (MWD); pain-free walking distance on a graded and constant-load treadmill; and HQL, measured using the Walking Impairment Questionnaire (WIQ) and the Medical Outcomes Study Short Form-36 (SF-36).

RESULTS: Maximal treadmill walking distance improved more in both cilostazol groups than in the placebo group (both $P < .0001$). WIQ and SF-36 physical summary scores improved significantly more with cilostazol than with placebo (for instance, WIQ distance score, $P < .0001$ and SF-36 physical summary score, $P < .0001$, comparing persons taking cilostazol with controls). Improved MWD correlated with improvements in WIQ (correlation with distance score, $r = 0.34$, $P < .0001$) and SF-36 physical summary scores ($r = 0.29$, $P < .0001$).

CONCLUSIONS: Treatment with cilostazol was associated with greater improvements in community-based walking ability and HQL in patients with intermittent claudication than treatment with placebo. These improvements correlated with increased MWD. This analysis of effects of cilostazol on improving walking ability in persons with claudication is the first cilostazol study focused on community-based measures of functional status and HQL. Questionnaires assessing walking ability and HQL provide important patient-based information about clinical outcomes of claudication therapy. **J Am Geriatr Soc 50:1939–1946, 2002.**

Key words: cilostazol; randomized controlled trial; treadmill exercise test; health-related quality of life; meta-analysis

From the *Department of Medicine, Divisions of Internal Medicine and Cardiology and Internal Medicine and Geriatrics, The University of Colorado Health Sciences Center, Denver, Colorado; †Health Assessment Laboratory, New England Medical Center Hospital, Boston, Massachusetts; ‡Cardiothoracic Surgery, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois; and §Otsuka America Pharmaceutical, Inc., Rockville, Maryland.

Dr. Judith Regensteiner has been on the speakers' bureau of Otsuka America, Pharm. Dr. Walter McCarthy has no relationship to Otsuka America. Dr John Ware has been an occasional consultant (unpaid) to Otsuka America. Dr. William Hiatt has been on a steering committee and speakers bureau of Otsuka America. Drs. William Forbes and Peter Forbes and Mr. Jeffrey Heckman work for Otsuka America.

Address correspondence to Judith G. Regensteiner, PhD, Section of Vascular Medicine, University of Colorado Health Sciences Center, 4200 East Ninth Avenue, Box B-180, Denver, CO 80262. E-mail: judy.regensteiner@uchsc.edu

Older patients with intermittent claudication secondary to peripheral arterial disease (PAD) have moderate to severe impairment of walking capacity that may limit their ability to meet the normal demands of daily living. In six recent multicenter trials, cilostazol improved pain-free walking distance (PFWD) and maximal treadmill walking distance (MWD).[1–6] However, treadmill testing does not completely characterize an intermittent claudication patient's response to treatment because it does not measure patients' perceived ability to walk in the community setting or their health-related quality of life (HQL).

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To more completely assess an intermittent claudication patient's response to a therapeutic intervention, questionnaires that evaluate functional status should be used. Examples of such tools include the Walking Impairment Questionnaire (WIQ), a disease-specific instrument for patients with PAD that was developed and validated against treadmill walking and is used to evaluate limitations in community-based walking ability,[7–9] and the Medical Outcomes Study Short Form-36 (SF-36),[10] a non–disease-specific questionnaire used to evaluate HQL in a variety of healthy and diseased populations. The predecessor of the SF-36, the SF-20, was validated against treadmill walking in a small group of intermittent claudication patients.[8]

In this analysis, data from the six studies described above were used to test the hypothesis that cilostazol would improve community-based walking ability and HQL in patients with moderate to severe intermittent claudication.[1–6] Relationships between changes in questionnaire measures and changes in walking distance measured by treadmill testing were also evaluated.

METHODS

Subjects

Data were accrued from subjects evaluated in six trials of cilostazol versus placebo to treat intermittent claudication (Table 1). Two thousand two hundred fifty-two persons were randomized into the studies, which were conducted from 1992 to 1997 (Figure 1). One patient withdrew before taking the first drug dose.[6] Other excluded subjects included 73 persons from one trial who received 150 mg cilostazol twice a day (bid)[5] and 232 people who received 400 mg pentoxifylline three times a day.[6] These two groups were excluded because the 150 mg dose of cilostazol is not an approved dose, and only one study included pentoxifylline. The groups included in this analysis were patients taking cilostazol 50 mg bid (n = 281), cilostazol 100 mg bid (n = 730), and placebo (n = 740). Thus, 1,751 patients were studied in the intent-to-treat population. No participant was included in more than one of the studies. The respective institutional review board approved each study at each site and all subjects gave informed consent to participate.

Patients aged 40 and older with a history of PAD longer than 6 months and a resting ankle/brachial index (ABI) of 0.90 or less were included. Patients must have had at least a 10 mmHg drop in ankle pressure after exercise and a reproducible maximal MWD during the baseline period.

Exclusion criteria were consistent among protocols.[1–6] Most notably, patients were excluded for having ischemic rest pain; ulceration or gangrene (indicating critical limb ischemia); uncontrolled blood pressure (BP) (i.e., supine arterial BP > 200 mmHg systolic or 100 mmHg diastolic); clinically significant bleeding within the past year; unstable angina pectoris; myocardial infarction, angioplasty, or coronary artery bypass graft (CABG) within the past 6 months; symptomatic cardiac arrhythmias; or unexplained syncopal episodes. Patients with Buerger's disease, limb threat or those with lower extremity arterial reconstruction (surgical or endovascular) or sympathectomy within the previous 3 months were ineligible for this study.

Patients were excluded if exercise was limited by any condition other than intermittent claudication, including, for example, congestive heart failure, angina pectoris, or arthritis. Patients were also excluded if they required antiplatelet agents other than aspirin, hemorheologic-modifying agents (e.g., pentoxifylline), or agents with significant effects on peripheral vessels, hemostasis, or platelet function. In addition, patients requiring uninterrupted use of warfarin or nonsteroi-

Table 1. Description of Study Protocols

Study Number	Duration (Weeks)	Treadmill Type	Treatment Group	n
92-202[1]	24	Constant load*	Cilostazol 100 mg bid	175
			Cilostazol 50 mg bid	171
			Placebo	170
201[2]	12	Graded†	Cilostazol 100 mg bid	95
			Placebo	94
94-203[3]	16	Graded†	Cilostazol 100 mg bid	119
			Placebo	120
94-201[4]	24	Constant load*	Cilostazol 100 mg bid	133
			Cilostazol 50 mg bid	132
			Placebo	129
95-201[5]	12	Constant load*	Cilostazol 150 mg bid	73
			Cilostazol 100 mg bid	72
			Placebo	70
96-202[6]	24	Graded†	Cilostazol 100 mg bid	228
			Pentoxifylline 400 mg tid	232
			Placebo	239

All studies included the Walking Impairment Questionnaire and Medical Outcomes Study Short Form-36 .
*2 mph, 12.5% grade.
†2 mph, 0% grade, increasing by 3.5% every 3 minutes.
bid = twice a day; tid = three times a day.

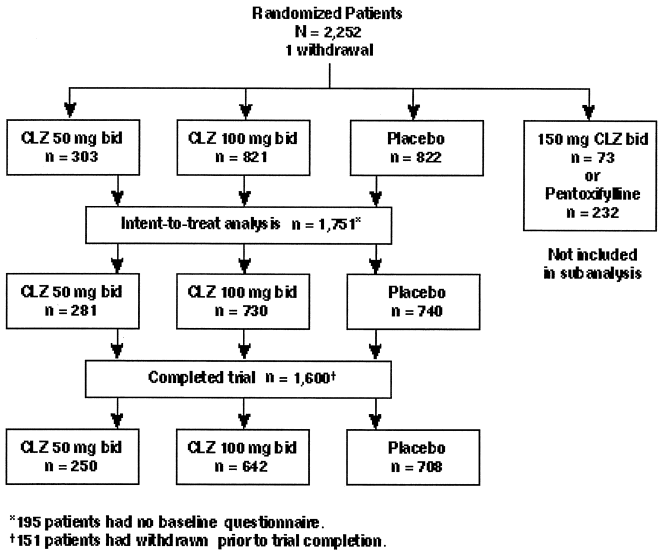

Figure 1. Flow diagram showing numbers of patients by treatment and dose in six randomized, double-blind, placebo-controlled, Phase 3 trials in patients treated with cilostazol (CLZ), pentoxifylline, or placebo. QOL = quality of life.

dal antiinflammatory agents (with the exception of ibuprofen at doses up to 1,200 mg/day) were excluded.

Patients were given the usual advice to treat intermittent claudication (i.e., to stop smoking and start exercise), but no formal program was included to address either of these goals.

Study Design

Data from all studies of the effects of cilostazol on walking ability in persons with claudication that included WIQ and SF-36 data were analyzed. Each trial had a multicenter, double-blind, placebo-controlled, parallel-group design. Patients were randomized to receive 50 or 100 mg cilostazol bid or placebo for 12,[2,5] 16,[3] or 24[1,4,6] weeks (Table 1). The group taking the 100 mg dose was the primary comparator group because this is the approved dose primarily prescribed for claudication. Data from the group taking 50 mg bid, the other approved dose used in two of the trials, are also reported but not included in the tables because this group was much smaller than the other two groups.

Treadmill Testing

Each trial used standardized treadmill testing procedures, which were consistent within each study. Two commonly used treadmill protocols were employed—graded and constant-load.[11,12] In the graded treadmill test (used in studies 2, 3, and 6 (Table 1)), subjects walked on the treadmill at an initial workload of 2 mph at a 0% grade for 3 minutes. Subsequent stages increased 3.5% in grade (without a change in speed) every 3 minutes to MWD. Constant-load testing (trials 1, 4, and 5 (Table 1)) was performed at 2 mph at a 12.5% grade until MWD was achieved. Pain-free walking distance was calculated as time walking on the treadmill until onset of claudication.

Ankle/Brachial Indices

ABIs were calculated as the ratio of the highest systolic BP in each ankle from the right or left posterior tibial or dorsalis pedis arteries divided by the highest brachial systolic BP, as previously reported.[3]

Functional-Status Questionnaires

A trained, central group of interviewers (Reilly Associates, Boca Raton, FL) administered all questionnaires by telephone to ensure standardization of data collection. To minimize the potential for bias in the self-evaluation of walking ability and functional status, the questionnaires were administered before treadmill testing on a separate day. Patients' questionnaire responses were thus not influenced by their treadmill exercise performance. Interviewers and patients were also blinded to previous questionnaire scores.

Walking Impairment Questionnaire

The WIQ (validated by comparison with treadmill walking in the PAD population) asked patients to assess the severity of their claudication pain, their perceived difficulty in walking defined distances and speeds, and their ability to climb stairs.[7–9] Responses to individual items within these categories were aggregated within a category into a single summary score, as previously described.[7,8] Symptom scores ranged from 0% (patients perceived much difficulty walking (very) due to pain in calves or buttocks) to 100% (patients perceived no difficulty walking (none) due to pain in calves or buttocks). Distance summary scores ranged from 0% (patients unable to walk 20 feet without stopping to rest) to 100% (patients able to walk five blocks without stopping to rest). Summary scores for walking speed ranged from 0% (patients unable to walk one block slowly without stopping to rest) to 100% (patients able to jog one block without stopping to rest). Stair-climbing scores ranged from 0% (patients unable to climb one flight of stairs without stopping to rest) to 100% (patients able to climb three flights of stairs without stopping to rest). The WIQ has been used to assess community-based walking ability in persons with claudication at baseline[7–9,13] and before and after treatments for claudication, including exercise rehabilitation, pharmacological treatments, peripheral bypass surgery, and angioplasty.[7,8,14]

Medical Outcomes Study Short Form-36

The SF-36, designed as a generic indicator of HQL for use in population surveys, has often been used in combination with disease-specific measures as an outcome measure. This questionnaire has been validated and found to be a reliable instrument for measuring HQL in large populations of healthy and diseased individuals.[8,10,15,16] The eight subscales measured by the SF-36 include physical functioning, role limitations—physical problems, general health perception, bodily pain, mental health, social functioning, role limitations—emotional problems, and vitality. Subscales are scored on a scale of 0% to 100%, where 0% equals the lowest level of functioning and 100% the highest. Subscales were also aggregated into physical summary scores and mental summary scores, as previously reported.[16,17] As in previous studies,[16,17] the physical and mental summary scores were standardized to have means of 50 and standard deviations of 10 in the general U.S. population.

Data Analysis

An intent-to-treat analysis was employed according to the last observation carried forward principle. Criteria for inclusion

in the analysis consisted of having at least one baseline and one postbaseline visit, including questionnaire data.

Questionnaire data from the six studies were pooled by treatment to assess the effects of study drug on the scores obtained with the instruments used to measure functional status and HQL (i.e., WIQ and SF-36 scores). The validity of pooling the data was statistically determined using the Q statistic for homogeneity.[18] Homogeneity of treatment effects for the questionnaire data was consistent across studies and is consistent with the lack of significance in the outcome of the Q statistic, thereby justifying pooling of studies ($P > .72$). An analysis of variance with post hoc tests was used to assess differences between treatment groups with respect to changes in treadmill walking distance and questionnaire scores from baseline to posttreatment.

Because two different types of treadmill protocols were used, mean MWD and PFWD values for each type are shown separately. In addition, each trial was of a different duration (12, 16, or 24 weeks). Percentage change was averaged across trials for each type of treadmill protocol to provide a summary of treatment effects on treadmill performance. No attempt was made to adjust for length of treatment.

Univariate correlations between treadmill walking and questionnaire variables were calculated using the Pearson product-moment correlation coefficient. Values are reported as mean ± standard deviation and considered significant when $P < .05$ in a two-tailed test. A stepwise multivariate regression model was used to evaluate independent predictors of walking ability in the whole group. No assumptions were made for missing questionnaire data, and no adjustments made for missing data in the analyses. All statistical analyses were performed by one of the authors (Dr. Zhang) using SAS Version 6.12 (SAS Institute, Inc., Cary, NC) on a Windows NT platform.

RESULTS

Demographic Variables

Of the 2,252 subjects initially enrolled in the six trials, 1,751 received the questionnaires at baseline and had at least one postbaseline questionnaire interview. Baseline demographic data for the three study groups did not differ (Table 2). The resting ABI, a primary marker of PAD hemodynamic disease severity, also did not differ between groups at baseline (data not shown). Likewise, risk factors and concomitant conditions did not differ between the placebo and cilostazol 100-mg bid groups (Table 2). The group taking 50 mg bid was included because this is an approved dose, but, because this group was only included in two studies and because the demographics are somewhat different between this group and the other two groups included, results are summarized separately below and are not included in the tables. More than 90% of patients in the three groups were current or previous smokers, diabetes mellitus was present in 26% to 28% of all subjects, and 56% to 65% of all patients had a history of hypertension.

Table 2. Demographic Characteristics, Risk Factors, and Concomitant Conditions

Characteristic	Placebo (n = 740)	Cilostazol 100 mg bid (n = 730)
Age, mean ± SD	65 ± 9	65 ± 9
Weight, kg, mean ± SD	81 ± 15	80 ± 16
Body mass index, kg/m², mean ± SD	27 ± 4	27 ± 4
Male, n (%)	566 (76.5)	563 (77.1)
Caucasian, n (%)	646 (87.3)	655 (89.7)
Risk factor, n (%)		
Cigarette smoking		
Never	50 (6.8)	56 (7.7)
Previous	51.5 (51.5)	57 (51.9)
Current	309 (41.8)	295 (40.4)
Diabetes mellitus	198 (26.8)	188 (25.8)
Hypertension	480 (64.9)	472 (64.7)
Cardiovascular risk*	576 (77.8)	562 (77.0)
Concomitant condition, n (%)		
Myocardial infarction	168 (22.7)	154 (21.1)
Angina pectoris	134 (18.1)	128 (17.5)
Stroke	37 (5.0)	27 (3.7)
Transient ischemic attack	54 (7.3)	50 (6.8)
Carotid endarterectomy	68 (9.2)	59 (8.1)

*Defined as having dyslipidemia, hypertension, current smoking, diabetes mellitus, or coronary heart disease. There were no significant differences between the two groups with regard to these variables.
SD = standard deviation; bid = twice a day.

Changes in Treadmill Exercise Performance with Treatment

Baseline and postbaseline values for MWD and PFWD on the graded treadmill protocol are shown in Table 3. MWD and PFWD improved over baseline with cilostazol and with placebo administration (all $P < .05$ compared with baseline), with the amount of change being consistently greater in the cilostazol group. Patients taking 100 mg bid of cilostazol increased their MWD (mean ± standard deviation) by 40% (100 ± 143 m) compared with a 20% (50 ± 127 m) increase for those taking placebo ($P < .0001$ for the difference in change from baseline to follow-up between groups, Figure 2). Similar results were observed for PFWD.

MWD and PFWD improved over baseline in both groups taking cilostazol and in the group taking placebo for the constant-load treadmill protocol (Table 3, all $P < .05$ compared with baseline). Patients taking 100 mg bid of cilostazol increased their MWD by 76% (95 ± 272 m) compared with a 20% (27 ± 113 m) change in the placebo group ((Figure 2) $P < .0001$ for the difference in change from baseline to follow-up between groups).

Overall, when data for both types of treadmill protocols were pooled, walking distances improved more in the cilostazol-treated groups than in the placebo-treated groups ($P < .0001$ for both MWD and PFWD).

Changes in Questionnaire Scores with Treatment

Walking Impairment Questionnaire

Improvements over baseline values were observed at the postbaseline time point in all WIQ scores in the group taking 100 mg bid of cilostazol (Table 4). In this group, patients reported that their walking distance had increased by 34%, walking speed by 21%, stair-climbing ability by 12%, and pain severity by 34% (all $P < .05$ vs baseline).

Table 3. Treadmill Walking Performance

Walking Distance (Meters)	Grand Protocol			Constant-Load Protocol		
	Baseline	Postbaseline		Baseline	Postbaseline	
	Mean ± SD		*P*-value†	Mean ± SD		*P*-value†
Maximal						
Placebo	252 ± 143	302 ± 189*		134 ± 121	161 ± 129*	
Cilostazol 100 mg bid	250 ± 146	350 ± 214*	<.0001	125 ± 64	220 ± 296*†	<.0001
Pain free						
Placebo	132 ± 84	185 ± 135*		69 ± 33	95 ± 70*	
Cilostazol 100 mg bid	127 ± 84	210 ± 143*	<.0001	67 ± 30	123 ± 125*	<.0001

*$P < .05$ difference between baseline and postbaseline.
†*P*-values of difference in change from baseline to postbaseline in the group taking cilostazol versus the placebo group.
SD = standard deviation; bid = twice a day.

Changes were also noted in WIQ scores in the placebo group over baseline values; walking distance in these subjects improved 21% and walking speed 8%, for example (both $P < .05$), but changes in all WIQ scores from baseline to postbaseline were significantly greater for those taking 100 mg bid of cilostazol than for those taking placebo (comparison between persons treated with cilostazol vs placebo, $P < .0001$ for WIQ distance, speed, and pain severity scores in terms of differences between changes in scores in the cilostazol group vs changes in the placebo group and $P = .0017$ for the stair-climbing score).

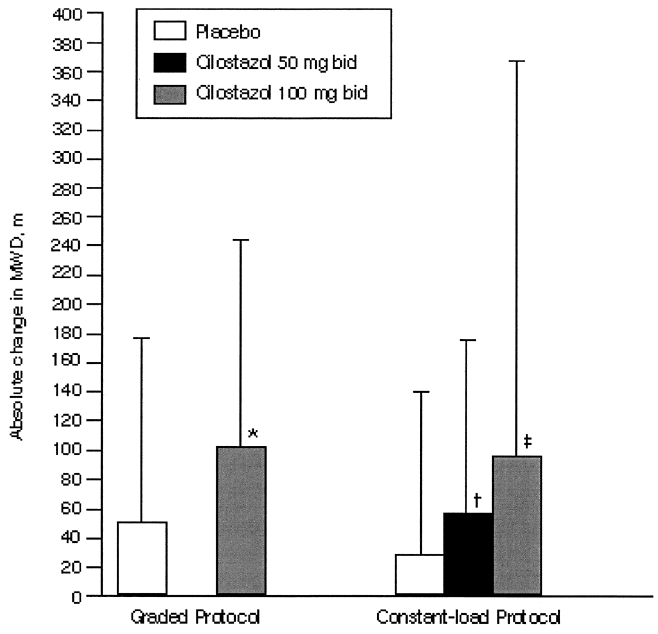

Figure 2. Changes in maximal walking distance (MWD), measured on a graded, constant-load treadmill, for patients receiving cilostazol 50 mg bid (n = 281), cilostazol 100 mg bid (n = 730), or placebo (n = 740). Graded protocols did not include a 50-mg group. Data shown are mean ± standard deviation. *$P < .0001$ vs placebo; †$P < .0011$ vs placebo; ‡$P < .0001$ vs placebo. bid = twice a day.

Medical Outcomes Study Short Form-36

For those who received 100 mg bid of cilostazol, the SF-36 physical summary score improved 5% ($P < .05$ (Table 5)). Three of the subscales making up this summary score improved as well, including physical functioning (9%), role limitations/physical problems (6%), and bodily pain (7%) (all $P < .05$ (Table 6)). The mental summary score did not improve from baseline, although one subscale, the mean vitality score, improved significantly ($P < .05$) from 53 ± 21 to 55 ± 22 (mental subscales not shown). Subjects who received placebo improved their physical function score significantly ($P < .05$), although to a lesser extent than patients taking cilostazol. The physical summary score, physical function score, role limitations/physical problems score, and bodily pain score all improved more in the group taking cilostazol 100 mg bid than in the group who received placebo ($P < .0001$ for differences between changes in SF-36 scores for the 100-mg bid cilostazol group vs changes for the placebo group for the physical summary and physical function scores, $P = .0013$ for role limitation/physical problems, and $P = .0003$ for bodily pain scores).

Summary of Data for Group Receiving 50 mg bid Cilostazol

The group receiving 50 mg bid cilostazol had a smaller percentage of patients with a history of angina pectoris ($P = .0370$), transient ischemic attack ($P = .0009$), hypertension ($P = .0263$), or previous carotid endarterectomy ($P = .0027$) than the other two groups (50 mg bid vs 100 mg bid of cilostazol and placebo). Similar to the 100-mg bid group, MWD improved more in the group taking 50 mg bid of cilostazol than placebo ($P < .0011$ (Figure 2)). With the exception of stair-climbing scores, which did not differ between groups, WIQ scores in this group also improved more than in placebo-treated patients ($P < .0001$ for distance and speed scores, $P = .0006$ for pain severity, data not shown). As in the 100-mg group, the physical summary score and most of its subscales on the SF-36 (other than the role limitations—physical problems score), but not mental summary scores or subscales, improved in the 50-mg group more than in placebo-treated patients (physical summary score, $P < .0028$; physical function score, $P < .0024$; bodily pain score, $P < .0097$).

Table 4. Walking Impairment Questionnaire

Score	Baseline	Follow-Up	Absolute Change	*P*-value†	Change %
	Meters, Mean ± Standard Deviation				
Walking distance					
Placebo	29 ± 26	35 ± 29	6 ± 25*		21
Cilostazol 100 mg bid	32 ± 27	43 ± 32	11 ± 27*	<.0001	34
Walking speed					
Placebo	37 ± 27	40 ± 27	3 ± 26*		8
Cilostazol 100 mg bid	39 ± 28	47 ± 30	8 ± 26*	<.0001	21
Stair climbing					
Placebo	47 ± 33	49 ± 33	2 ± 30		4
Cilostazol 100 mg bid	49 ± 33	55 ± 35	6 ± 28*	<.0017	12
Calf-pain severity					
Placebo	38 ± 25	47 ± 27	9 ± 28*		24
Cilostazol 100 mg bid	41 ± 24	55 ± 27	15 ± 28*	<.0001	34

*$P < .05$ compared with baseline value within group.
†*P*-values for difference in change from baseline to postbaseline in the group taking cilostazol versus the placebo group.
bid = twice a day.

Correlations Between Functional Status and Treadmill Walking

Changes in the SF-36 physical function score correlated significantly with changes in MWD ($r = 0.33$, $P < .0001$). The correlation between changes in the overall physical summary score and changes in MWD was $r = 0.29$ ($P < .0001$). Changes in WIQ scores also correlated with changes in MWD. For instance, the correlation between change in the WIQ walking distance score and change in MWD was $r = 0.34$ ($P < .0001$).

The multivariate regression model was developed using a step-wise process. Variables in the final model included walking distance, limitation in walking due to calf pain severity, stair climbing (all from the WIQ) vitality, social function, general health perception, role limitations—emotional problems, and physical function (from the SF-36). Multivariate regression analyses and forward regression model selections showed that, across all groups, changes in baseline walking distance and calf pain severity scores on the WIQ and baseline physical function score on the SF-36 were independent predictors of change in MWD. The coefficient of determination for the model was 0.19 ($P < .0001$).

DISCUSSION

In patients with disabling intermittent claudication due to PAD, treatment with cilostazol resulted in greater improvements in community-based walking ability and functional status than did placebo. These improvements were associated with increases in treadmill-assessed MWD, an objective endpoint.

Treadmill walking tests are considered the best objective measure of functional ability in patients with intermittent claudication, but such tests do not address the generalizability of an intervention's benefit in the community setting in terms of performing normal daily activities. The questionnaires used in the reported studies are not solely a surrogate for treadmill walking. To the contrary, these questionnaires also examine the effects of a treatment (in this case, a drug) on a broader range of social and role performance that represents HQL. The analysis for this report represents the first study in persons with claudication

Table 5. Medical Outcomes Study Short Form-36 Summary Scores

Summary Score	Baseline	Follow-up	Absolute Change	*P*-value†	Change %
	Mean ± Standard Deviation				
Physical					
Placebo	36 ± 10	36 ± 10	0		0
Cilostazol 100 mg bid	36 ± 10	38 ± 10	2 ± 9*	<.0001	5
Mental					
Placebo	56 ± 9	56 ± 10	0		0
Cilostazol 100 mg bid	56 ± 9	55 ± 10	1	.2832	2

Note: These scores are normed based on a mean of 50 and SD of 10.
*$P < .05$ compared with baseline value within group.
†*P*-values for difference in change from baseline to postbaseline in the group taking cilostazol versus the placebo group.
bid = twice a day.

Table 6. Medical Outcomes Study Short Form-36: Physical Subscales

Physical Subscale	Baseline	Follow-Up	Absolute Change	*P*-value†	Change %
	Mean ± Standard Deviation				
Physical function					
Placebo	51 ± 21	53 ± 23	2 ± 19*		2
Cilostazol 100 mg bid	54 ± 21	59 ± 23	5 ± 19*	<.0001	9
Role limitations, physical problems					
Placebo	53 ± 38	51 ± 39	−2 ± 39		6
Cilostazol 100 mg bid	54 ± 38	57 ± 39	3 ± 37*	.0013	6
Bodily pain					
Placebo	56 ± 22	56 ± 24	0		0
Cilostazol 100 mg bid	56 ± 22	60 ± 24	4 ± 23*	.0003	7
General health perception					
Placebo	58 ± 21	57 ± 22	−1 ± 15		2
Cilostazol 100 mg bid	58 ± 21	58 ± 21	0.1 ± 15.0	.0957	0

*$P < .05$ compared with baseline value within group.
† *P*-values for difference in change from baseline to post-baseline in the group taking cilostazol versus the placebo group.
bid = twice a day.

treated with cilostazol that is focused on functional status and HQL effects of cilostazol and reveals that a pharmacological therapy can lead to improvement in community-based measures of function in persons with claudication. In addition, this report affirms the relationship between a laboratory-based measure of functional ability (treadmill testing) and community-based measures (the questionnaires).

In part, the analysis of the present report was enabled by the large sample size resulting from including patients from six trials. Although including patients from multiple studies induces possible sources of error, it should be noted that the inclusion and exclusion criteria were consistent among these trials. In addition, a trained interviewer from the same company administered all questionnaires were by telephone. In addition, statistical evaluation ensured that interstudy data were appropriately homogeneous to enable pooling for treadmill testing and HQL evaluation.

Patients in both cilostazol and placebo groups had improved treadmill walking and improvements in some questionnaire variables for both questionnaires, but, despite this placebo effect, the benefits of cilostazol in terms of these variables were significantly greater than those of placebo for treadmill and questionnaire data. Thus, questionnaire scores actually reflected treadmill results for treated and placebo groups by showing the differing degrees of improvement achieved by the respective treatments. A placebo effect on walking ability measured by treadmill has previously been observed in control groups of studies designed to assess treatments for intermittent claudication.[19]

For any study in which questionnaire data are used to assess functional status, questions arise about the validity and sensitivity of the questionnaires used. The validity of patient-based assessments depends on selection of the appropriate performance domains and a wide range of subjects for study, validation of the performance domains against other measures, and use of measures that are feasible, reproducible, and sensitive to change with treatment. The correlations between treadmill measures and questionnaire measures (although expected) were reassuring in this study. Other issues may include questions about generalizability of the results because of exclusion of patients from study. Exclusions during screening occurred for a number of reasons, including walking too long or too short a time during the initial screening treadmill tests and comorbid conditions such as those defined in the Methods section. Reasons for exclusions were similar between placebo and cilostazol-treated patients.

The WIQ and SF-36 were chosen for use in this study because of prior validation and use in the PAD population.[7–9,13,14] It has been reported that the WIQ and the SF-36 (or SF-20) correlated with measures of treadmill walking, including MWD at baseline and after interventions such as exercise training, peripheral bypass surgery, and angioplasty.[7–9,13] Although the WIQ and SF-36 had been validated before with other types of treatments for claudication, this was the first time that these questionnaires were used before and after a pharmacological therapy for claudication, and it was found that the questionnaires were strongly correlated with measures of treadmill walking with this treatment. The WIQ is a disease-specific questionnaire used in patients with PAD who have intermittent claudication.[7–9] The SF-36 questionnaire has been used in more than 1,500 published studies in which evaluation of HQL in more than 130 diseased populations[20] has included patients with PAD.[8]

The relative ease of using validated questionnaires to measure community-based walking ability and HQL is important for a large study. Another important matter is to determine whether the questionnaires address the relevant domains. In the present study, most of the improvement was in physical functioning, specifically, in activities requiring ambulation, rather than in social or mental domains. This reflects a finding observed previously about the sensitivity of SF-36 physical domain measures to the specific limitations imposed by intermittent claudication. PAD is a disease that limits normal ambulatory activities. Previous studies have also shown that the greatest im-

provements after treatment for intermittent claudication are in the area of physical functioning.[8] Furthermore, patients with intermittent claudication typically do not differ from age-matched controls in terms of mental health, as measured by the SF-36; therefore, improvement in that area was not expected using that instrument. Alternatively, the sensitivity of the SF-36, which is not disease specific, to the domains covered by the mental summary score may be less than its sensitivity to the physical summary score domains in patients with claudication. Thus, aspects of quality of life affected by claudication may not be adequately assessed by the SF-36. Other questionnaires are currently under development to assess these domains in greater depth.

In contrast, the physical summary score of the SF-36 improved significantly with cilostazol, as did the three subscales that are weighted highest in estimating that summary score. Results are thus consistent with a significant improvement in physical functioning that went hand in hand with improvements in participation in usual role activities. In relation to published criteria that have been used to interpret the SF-36 summary measures, average changes in the physical summary score in the amount of 2 points, which is 0.2 of a standard deviation, should be considered clinically and socially relevant.[21] For example, a change of that amount is roughly equivalent to the amount of physical decline associated with 2 years of aging in a population of the same age as the study participants. Differences in scores of this amount have also been linked to performance of recreational and social activities and participation in daily activities that constitute the usual role of these patients in everyday life. Thus, cilostazol benefited measures of HQL in a clinically significant way. The loss of functional capacity normally associated with PAD becomes especially critical with aging when functional range is narrowed, even in the relative absence of disease. Therefore, the availability of treatments to improve functional capacity is of great importance.

It is important to ask whether the HQL improvements seen in patients taking cilostazol are meaningful to patients. The questionnaires used help address the questions, "How does disease affect functioning?" and "Can treatment improve functioning?" With the focus on HQL rather than the somewhat amorphous "quality of life," the results of the questionnaires after treatment with cilostazol suggest that patients may be able to accomplish more in everyday life after treatment than before.

Compelling reasons thus exist to assess functional status in clinical trials of intermittent claudication treatments. Future studies should further evaluate the effect of drugs for the treatment of intermittent claudication on patients' normal daily activities and on their HQL.

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