

# A New Pharmacological Treatment for Intermittent Claudication:

## Results of a Randomized, Multicenter Trial

Hugh G. Beebe, MD; David L. Dawson, MD; Bruce S. Cutler, MD; J. Alan Herd, MD; D. Eugene Strandness, Jr, MD; Enoch B. Bortey, PhD; William P. Forbes, PharmD

**Background:** Effective medication is limited for the relief of intermittent claudication, a common manifestation of arterial occlusive disease. Cilostazol is a potent inhibitor of platelet aggregation with vasodilation effects.

**Objective:** To evaluate the safety and efficacy of cilostazol for the treatment of intermittent claudication.

**Methods:** Thirty-seven outpatient vascular medicine clinics at regional tertiary and university hospitals in the United States participated in this multicenter, randomized, double-blind, placebo-controlled, parallel trial. Of the 663 screened volunteer patients with leg discomfort, a total of 516 men and women 40 years or older with a diagnosis of moderately severe chronic, stable, symptomatic intermittent claudication were randomized to receive cilostazol, 100 mg, cilostazol, 50 mg, or placebo twice a day orally for 24 weeks. Outcome measures included pain-free and maximal walking distances via treadmill testing, patient-based quality-of-life measures, global assessments by patient and physician, and cardiovascular morbidity and all-cause mortality survival analysis.

**Results:** The clinical and statistical superiority of active treatment over placebo was evident as early as week 4, with continued improvement at all subsequent time points. After 24 weeks, patients who received cilostazol, 100 mg, twice a day had a 51% geometric mean

improvement in maximal walking distance ( $P < .001$  vs placebo); those who received cilostazol, 50 mg, twice a day had a 38% geometric mean improvement in maximal walking distance ( $P < .001$  vs placebo). These percentages translate into an arithmetic mean increase in distance walked, from 129.7 m at baseline to 258.8 m at week 24 for the cilostazol, 100 mg, group, and from 131.5 to 198.8 m for the cilostazol, 50 mg, group. Geometric mean change for pain-free walking distance increased by 59% ( $P < .001$ ) and 48% ( $P < .001$ ), respectively, in the cilostazol, 100 mg, and cilostazol, 50 mg, groups. These results were corroborated by the results of subjective quality-of-life assessments, functional status, and global evaluations. Headache, abnormal stool samples or diarrhea, dizziness, and palpitations were the most commonly reported potentially drug-related adverse events and were self-limited. A total of 75 patients (14.5%) withdrew because of any adverse event, which was equally distributed between all 3 treatment groups. Similarly, there were no differences between groups in the incidence of combined cardiovascular morbidity or all-cause mortality.

**Conclusion:** Compared with placebo, long-term use of cilostazol, 100 mg or 50 mg, twice a day significantly improves walking distances in patients with intermittent claudication.

*Arch Intern Med.* 1999;159:2041-2050

From the Jobst Vascular Center, Toledo, Ohio (Dr Beebe); Wilford Hall Medical Center (Dr Dawson), Lackland Air Force Base, San Antonio, Tex; University of Massachusetts Medical Center (Dr Cutler), Worcester; The Methodist Hospital, Houston, Tex (Dr Herd); University of Washington Medical School, Seattle (Dr Strandness); and Otsuka America Pharmaceutical Inc, Rockville, Md (Drs Bortey and Forbes). A complete list of study investigators appears on page 2049.

**I** NTERMITTENT claudication is a debilitating condition that severely restricts a person's ability to walk and thus, to perform ordinary daily activities of independent living. Intermittent claudication, a pain or ache in muscle groups of the lower limbs that occurs with walking and subsides with rest, is caused by a deficient blood supply in exercising muscle and is associated with lower extremity arterial occlusive disease.<sup>1</sup> In the United States, lower extremity arterial occlusive disease may affect up to 20% of the older adult population.<sup>2</sup> Approximately 70% of patients with lower extremity arterial occlusive disease present with claudication as

their sole symptom.<sup>3</sup> A patient with intermittent claudication may experience a progressive decline in physical functioning—as the claudication worsens, the less the patient walks; the less the patient exercises, the more general cardiovascular status deteriorates.

In the United States, the most common pharmacological approach to intermittent claudication is pentoxifylline. Additional classes of drugs include vasodilators, antiplatelet agents, anticoagulants, prostaglandins, and prostaglandin analogs that have been suggested or tested as possible treatment for claudication and vary in result. Clinical trials demonstrating the effectiveness of all these

## PATIENTS AND METHODS

### STUDY DESIGN

This multicenter, randomized, double-blind, 24-week, placebo-controlled, parallel trial assessed the safety and efficacy of cilostazol, 100 mg or 50 mg, taken orally twice a day in relieving intermittent claudication. A total of 37 outpatient vascular clinics in tertiary hospitals and medical schools throughout the United States participated. Men and women 40 years or older who had at least a 6-month history of stable, symptomatic intermittent claudication secondary to lower extremity arterial occlusive disease, who demonstrated reproducible walking distances on screening treadmill tests, and who terminated all screening treadmill tests solely because of claudication pain, were eligible for inclusion in the study. During a minimum 3-week screening period, patients had to demonstrate evidence of stable disease by having pain-free walking distance (initial claudication distance) results between 30 and 200 m on 2 consecutive treadmill tests, with 25% or more variance between results. The treadmill test was a constant-rate, constant-grade design with a 12.5% incline and speed of 3.2 km/h (2 mph). Additional entry criteria were a resting ankle brachial index of 0.90 or less and a 10 mm Hg or more decrease in ankle artery blood pressure following the onset of maximal walking distance (absolute claudication distance).

Exclusionary criteria included ischemic pain at rest, gross obesity, childbearing potential, hypertension (>200 mm Hg systolic or >100 mm Hg diastolic supine resting blood pressure), current metastatic malignant neoplasm, exercise-limiting cardiac disease, and history of bleeding tendencies, as well as concomitant use of antiplatelet, anticoagulant, vasoactive, hemorrheologic, or nonsteroidal anti-inflammatory agents. Occasional use of acetaminophen, diclofenac sodium, or nitroglycerin was allowed. Before undergoing screening procedures, patients signed an informed consent form approved by the institutional review board at each participating center.

The sample size required to ensure 80% power of detecting a doubling of the cardiovascular morbidity and all-cause mortality event rate was 143 patients per group, based on a 5% significance level (2-sided). Therefore, enrollment was set at 150 patients per treatment group to show a between-group difference in the combined end point of morbidity and mortality. Because fewer patients were needed for the primary efficacy end point of improvement in treadmill walking distances, the protocol allowed 8 investigational centers to waive the requirement for patients randomized at their centers to undergo treadmill testing and Doppler-measured limb pressure assessments. These randomized patients, primarily monitored for safety and exempt from efficacy treadmill testing and Doppler data, underwent all other assessments and were evaluated for safety the same as the non-exempt patients (ie, those monitored for safety plus efficacy treadmill testing).

### ASSIGNMENT AND BLINDING

On completing the screening period, eligible patients were randomized to double-blind treatment with 50 mg or 100 mg of cilostazol or placebo. Randomization of eligible patients was stratified by each clinical center. A master randomization list of patient code assignments to the test medications (100 mg, 50 mg, or placebo) was developed using a permuted-block design. The master list was then forwarded to the drug packaging company, where a separate medication supply was prepared for each unique patient code. All 3 test medications had a similar appearance. Patient compliance with study medication was assessed by having the patient return all used and unused treatment cards at each scheduled dispensing visit.

### PATIENT EVALUATION

Patients were evaluated 3 times at baseline and at weeks 4, 8, 16, 20, and 24. Efficacy evaluations included exercise treadmill testing assessments of pain-free and maximal walking distances; Doppler-measured bilateral peripheral limb pressures assessed before exercise and 1, 5, and 9 minutes following

agents are limited. Medical therapy has routinely included exercise programs and the modification of risk factors such as smoking, sedentary lifestyle, and diet, but patient participation and compliance are often disappointing. Arterial bypass or percutaneous transluminal angioplasty may be appropriate and effective for some patients with severe, incapacitating claudication.<sup>4</sup> However, these procedures are not indicated for the many patients whose severity of intermittent claudication does not warrant the attendant risks of invasive procedures. An effective medication that clearly improves physical functioning could provide an important addition to the limited therapeutic armamentarium currently available.

Cilostazol (6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone, OPC-13013, CAS 73963-72-1) is a type III phosphodiesterase inhibitor. Although its mechanism of action is not fully un-

derstood, cilostazol is thought to inhibit cyclic adenosine monophosphate phosphodiesterase, which leads to an increase in cyclic adenosine monophosphate in platelets and blood vessels, and to promote the effect of prostaglandin I<sub>2</sub>, an endothelial cell-derived substance that inhibits platelet aggregation and relaxes vascular smooth muscle. Cilostazol is an antithrombotic agent that inhibits platelet aggregation and increases vasodilation. Its antiplatelet activity is 10 to 30 times more potent than aspirin.<sup>5</sup>

This study evaluated the safety and efficacy of cilostazol in relieving intermittent claudication. We sought to find whether cilostazol, 100 mg and 50 mg, taken orally twice a day, will significantly improve the pain-free and maximal walking distances among individuals with intermittent claudication when compared with baseline and placebo.

exercise; quality-of-life and functional status questionnaires, and patient and physician end-of-treatment global therapeutic assessments. A survival analysis of combined all-cause mortality and cardiovascular morbidity was done. For all-cause mortality and cardiovascular morbidity assessment, an independent study committee, blinded to treatment assignment, adjudicated all patient deaths and serious adverse events according to protocol-defined criteria (**Table 1**). Additional safety assessments included adverse events, vital signs, physical examination findings, clinical laboratory results, electrocardiograms, and 48-hour Holter monitoring.

The functional status questionnaires, administered by centralized telephone interview, included the Medical Outcomes Scale Short Form-36(SF-36)—a generalized measure of quality of life, and 2 disease-specific questionnaires: the Walking Impairment Questionnaire (WIQ) and Claudication Outcome Measures (COM). The SF-36 includes 8 subscales that measure patients' perception of their health status in 3 main areas: (1) physical health concepts (bodily pain, physical function, and role-physical); (2) mental health concepts (social functioning, role-emotional, and mental health); and (3) combined physical-mental health concepts (general health perception and vitality).<sup>6</sup> The WIQ characterizes walking speed, walking distance, and symptoms associated with walking difficulty to assess the degree of walking impairment and efficacy of therapeutic intervention in improving walking ability.<sup>7</sup> The COM assesses the severity of walking pain and discomfort while walking short and long distances, the degree to which claudication pain imposes physical limitations, and the extent to which the pain affects daily and social activities or causes worry and concern. The COM questionnaire was developed by the study sponsor and has not been independently validated. Scores were arranged so that a higher score was always indicative of better functioning.

## STATISTICAL ANALYSIS

All statistical analyses were based on the intent-to-treat population (ie, patients having a baseline and at least one post-baseline assessment). For safety analyses, this included all

516 randomized patients. Demographic, medical history, and baseline data were summarized by treatment group and analyzed for comparability across groups using the Kruskal-Wallis test for continuous variables and the Cochran-Mantel-Haenszel test for categorical variables.

The primary efficacy variables were pain-free and maximal walking distances at week 24. To reduce the variability that is typically seen with walking distance data and the impact of extreme values, pain-free and maximal walking distances were analyzed primarily in terms of the logarithm of the ratio of distance walked over distance walked at baseline. Log transformation allowed analysis of all patient data, since there was no justification for discarding extreme observations. If the Kruskal-Wallis test for these variables was significant, a Wilcoxon rank sum test<sup>8</sup> for pairwise comparisons was performed. The *P* values for the pairwise tests, cilostazol, 100 mg, vs placebo and cilostazol, 50 mg, vs placebo, were considered the primary inferential evidence, and a *P* value of .05 or less was considered statistically significant. The per-protocol primary analysis for analyzing treadmill data was last observation carried forward, in which the postrandomization values were carried forward to populate the missing visit data. In addition to the analysis using log transformation, walking distance in meters was provided for a longitudinal clinical perspective.

Secondary efficacy variables included functional status questionnaires, global therapeutic assessment, and survival analysis of combined cardiovascular morbidity and all-cause mortality. For the quality-of-life and patient questionnaires, repeated-measures analysis of variance was used and treatment comparisons were performed using the Kruskal-Wallis and Wilcoxon rank sum tests on change from baseline values. Between-group differences in the global therapeutic assessment were evaluated by the Cochran-Mantel-Haenszel<sup>9</sup> test and in the combined cardiovascular morbidity and all-cause mortality end point by the Kaplan-Meier product limit estimator.

In the analysis of safety data, changes in safety variables from baseline were summarized using descriptive statistics and shift tables as appropriate. A 2-sided Fisher exact test<sup>8</sup> was used to assess adverse events between groups.

## RESULTS

### PATIENT DISPOSITION

As shown in the flow diagram of patient disposition (**Figure 1**), 663 patients were screened for eligibility, 516 of whom were randomly assigned to treatment: 175 patients received cilostazol, 100 mg, twice a day, 171 patients received cilostazol, 50 mg, twice a day, and 170 patients received placebo. All 516 patients were assessed for safety. A subgroup of 419 patients (safety and efficacy subgroup), which represented 81.2% (419/516) of the randomized population, were included in the efficacy intent-to-treat analysis of treadmill data. The additional 97 patients (safety-only subgroup), who were randomized but did not undergo postrandomization treadmill tests, were equally dis-

tributed between treatments. Of the 419 patients in the efficacy intent-to-treat group, 316 (75.4%) completed all treadmill visits up to week 24. The 98 patients (18.9%) who withdrew from study participation, 75 (14.5%) of whom because of any adverse events, were also equally distributed between treatment groups.

Demographic data are shown in **Table 2**. Randomized patients were primarily white (88.6%) and male (76.0%), with an average age of 64.6 years (range, 41-88 years). A total of 93.4% (482/516) of patients had a positive history for cigarette smoking, and more than one third were current smokers. Patients with diabetes accounted for 28.1% (145/516) of the population. There were no clinically or statistically relevant differences between the treatment groups at baseline.

**Table 1. Protocol-Defined Criteria for Cardiovascular Morbidity**

1. Myocardial infarction verified by clinical symptoms, enzyme changes, and electrocardiogram changes indicative of myocardial infarction
2. Cerebrovascular infarct (stroke) verified by neurologic deficit lasting longer than 24 hours confirmed by angiography, computed tomographic scan, or magnetic resonance imaging
3. Arterial revascularization, including angioplasty or surgical vascular reconstruction:
  - a. Procedures for peripheral vascular disease, including lower extremity bypass\*
  - b. Other procedures, including coronary artery bypass graft, carotid endarterectomy, and renal procedures\*
4. Amputation for ischemia

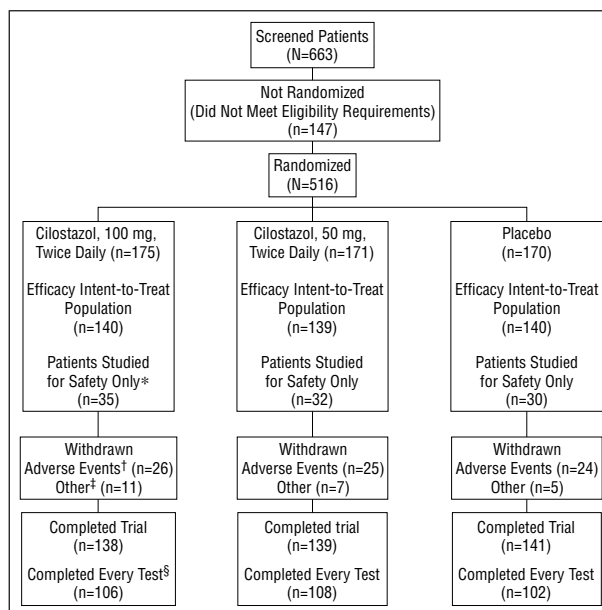
\*Both 3a and 3b classifications were defined by the executive committee post hoc to clarify outcomes.

### TREADMILL DATA

**Table 3** shows the results of the primary efficacy analysis of treadmill data and geometric mean change from baseline using last observation carried forward at week 24, as well as secondary results at the interim time points of weeks 4, 8, 16, and 20. For ease of interpretation, geometric mean change can be converted to geometric mean percent change by the following simple calculation: Geometric Mean Percent Change =  $[(\text{Geometric Mean}) - 1] \times 100$ .

At week 24, pain-free and maximal walking distances were statistically significantly greater in both cilostazol groups compared with the placebo group. At week 24, the improvement in pain-free walking distance was 59% in the cilostazol, 100 mg, group and 48% in the cilostazol, 50 mg, group compared with 20% in the placebo group ( $P < .001$  for cilostazol, 100 mg, twice a day vs placebo and  $P < .001$  for cilostazol, 50 mg, twice a day vs placebo). Results were similar for maximal walking distance at week 24, with patients in both cilostazol groups showing improvement: 51% in the cilostazol, 100 mg, group and 38% in the cilostazol, 50 mg, group, compared with 15% in the placebo group ( $P \leq .001$  for cilostazol, 100 mg, twice a day vs placebo;  $P < .001$  for cilostazol, 50 mg, twice a day vs placebo).

The superiority of active treatment over placebo was observed as early as week 4 and was maintained at all subsequent time points up to week 24. As shown in **Figure 2** and **Figure 3**, the magnitude of improvement in both pain-free and maximal walking distances increased over time. Also shown in Table 3 is the mean walking distance in meters walked, which reinforces the significance of the geometric mean change data. Patients taking cilostazol, 100 mg, twice a day nearly doubled their walking distances on the treadmill after 24 weeks of treatment, from a pain-free walking distance of 70.4 m at baseline to 137.9 m at week 24, and a maximal walking distance of 129.7 m at baseline to 258.8 m at week 24. Patients taking cilostazol, 50 mg, twice a day increased their walking distances greater than 1.5-fold after 24 weeks of treatment, from a pain-free walking distance of 66.5 m at baseline to 115.1 m at week 24, and a maximal walk-



**Figure 1.** Disposition of patients in the trial. Asterisk indicates patients did not undergo postrandomization treadmill testing; dagger, adverse event, death, or marked deterioration; double dagger, failed screening, inability to continue, noncompliance, or lack of response to study drug; and section mark, patients from efficacy intent-to-treat population who completed all treadmill visits.

ing distance of 131.5 m at baseline to 198.8 m at week 24. Treatment-by-center interactions were investigated and showed no significance.

### FUNCTIONAL STATUS QUESTIONNAIRES

Improvements in walking distances were paralleled by patients' perceived physical improvements, as assessed by the SF-36, WIQ, and COM. **Table 4** summarizes results of the functional status questionnaires at week 24. For the physical health concepts domain of the SF-36, both cilostazol groups were significantly superior to placebo at week 24 in the physical function and bodily pain scales. The role-physical domain improved in the cilostazol groups, although it did not reach statistical significance. There was no significant difference between either cilostazol group and placebo for the mental health concepts domain. For the WIQ at week 24, both cilostazol groups were superior to placebo for walking speed and walking distance. Statistically significant improvements were seen in the following COM scales: walking pain/discomfort, change in walking pain/discomfort, and walking pain/discomfort related to ability to perform physical activities. For all other domains and subscales, the cilostazol groups were not significantly different from the placebo group.

### GLOBAL THERAPEUTIC ASSESSMENT

Generally, more patients and investigators judged claudication symptoms at the end of treatment to have been improved by cilostazol than by placebo (**Table 5**). Significantly more patients in both cilostazol groups rated their outcomes as "better" or "much better" compared with pretreatment: 53.2% in the cilostazol, 100 mg, group,

**Table 2. Demographics of All Randomized Patients**

Parameter	Cilostazol, 100 mg, Twice Daily (n = 175)	Cilostazol, 50 mg, Twice Daily (n = 171)	Placebo (n = 170)	P*
Age, y				
Mean ± SE	64.3 ± 8.5	64.5 ± 9.9	65.1 ± 9.3	.67
Range	42-85	41-88	41-86	
Age category, No. (%)				
<65 y	82 (46.9)	77 (45.0)	75 (44.1)	.87
≥65 y	93 (53.1)	94 (55.0)	95 (55.9)	
Sex, No. (%)				
Male	130 (74.3)	131 (76.6)	131 (77.1)	.81
Female	45 (25.7)	40 (23.4)	39 (22.9)	
Race, No. (%)				
White	154 (88.0)	152 (88.9)	151 (88.8)	.57
Black	15 (8.6)	17 (9.9)	15 (8.8)	
Hispanic	3 (1.7)	2 (1.2)	4 (2.4)	
Asian	2 (1.1)	0 (0)	0 (0)	
Other	1 (0.6)	0 (0)	0 (0)	
Weight, kg				
No.	175	171	170	.83
Mean ± SE	78.6 ± 16.1	79.6 ± 15.5	78.8 ± 16.0	
Range	41.8-115.0	42.0-132.7	47.7-129.4	
Height, cm				
No.	175	171	170	.88
Mean ± SE	171.6 ± 9.5	172.2 ± 9.4	171.9 ± 8.9	
Range	142.0-193.0	146.0-196.0	152.0-196.0	
Diabetes, No. (%)				
Yes	46 (26.3)	51 (29.8)	48 (28.2)	.76
No	129 (73.7)	120 (70.2)	122 (71.8)	
Cigarettes, No. (%)				
Never	12 (6.9)	11 (6.4)	11 (6.5)	.45
Previous	102 (58.3)	98 (57.3)	84 (49.4)	
Current	61 (34.9)	62 (36.3)	75 (44.1)	
Pack-years†				
No.	163	160	158	.14
Mean ± SE	51.4 ± 25.0	47.3 ± 28.2	47.5 ± 26.5	
Range	5.0-160.0	1.0-175.0	0.6-120.0	
Other tobacco products, No. (%)				
Never	152 (86.9)	153 (89.5)	154 (90.6)	.36
Previous	17 (9.7)	17 (9.9)	13 (7.6)	
Current	6 (3.4)	1 (0.6)	3 (1.8)	
Alcohol, No. (%)				
Never	24 (13.7)	28 (16.4)	23 (13.5)	.86
Previous	45 (25.7)	45 (26.3)	50 (29.4)	
Current	106 (60.6)	98 (57.3)	97 (57.1)	

\*Fisher exact test for categoric variables and Wilcoxon rank sum test for continuous variables.

†Pack-years indicates packs of cigarettes per day times number of years smoked.

54.1% in the cilostazol, 50 mg, group, and 37.3% in the placebo group ( $P = .002$  for cilostazol, 100 mg, twice a day vs placebo;  $P = .01$  for cilostazol, 50 mg, twice a day vs placebo). Significantly more investigators evaluating patients in the cilostazol, 100 mg, group vs placebo also rated improvement as “better” or “much better” (48.5% vs 33.1%;  $P = .003$ ).

#### CARDIOVASCULAR MORBIDITY AND ALL-CAUSE MORTALITY

A life-table analysis was performed to determine any between-group differences in the incidence of combined cardiovascular morbidity and all-cause mortality. A total of 34 patients met the criterion of cardiovascular morbidity ( $n = 29$ ) or all-cause mortality ( $n = 5$ ) as determined

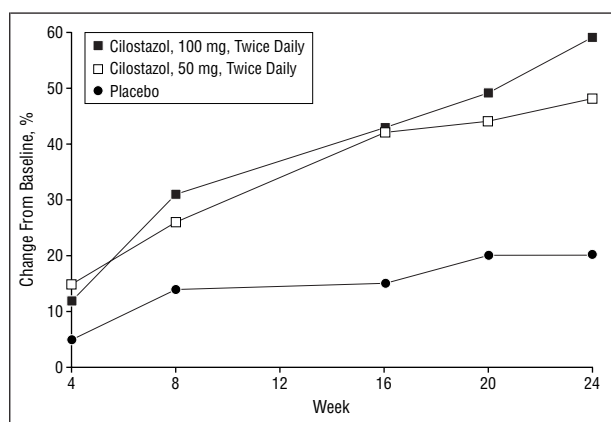
by the executive committee (**Table 6**). **Figure 4** depicts the results of the life-table analysis and illustrates no statistically significant differences between treatment groups in the probability of survival without cardiovascular morbidity or all-cause mortality during 24 weeks of therapy ( $P = .71$ ).

#### SAFETY

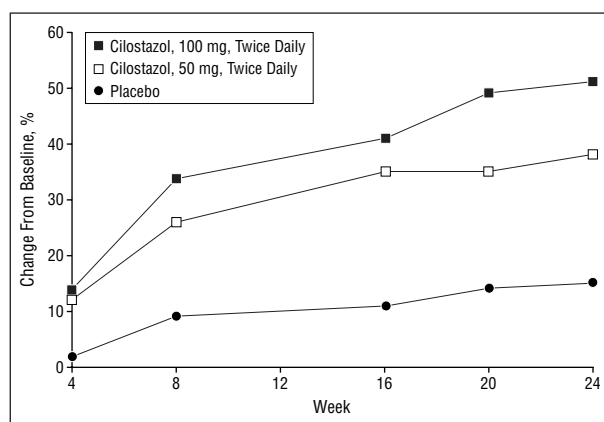
The most common ( $\geq 10\%$  incidence) adverse events judged by investigators to be potentially drug related were headache, abnormal stool samples (ie, loose and soft stool samples), diarrhea, dizziness, and palpitation (**Table 7**). Patients who received cilostazol reported a significantly greater incidence of headache, abnormal stool samples, diarrhea, and palpitation than patients who received pla-

**Table 3. Treadmill Test Results in the Efficacy Intent-to-Treat Population: Geometric Mean Change From Baseline and Mean Distance in Meters Using Last Observation Carried Forward**

Week	Geometric Mean Change From Baseline			Pairwise Comparison P Value		Mean Walking Distance in Meters (No.)		
	Cilostazol, 100 mg, Twice Daily	Cilostazol, 50 mg, Twice Daily	Placebo	Cilostazol, 100 mg, Twice Daily vs Placebo	Cilostazol, 50 mg, Twice Daily vs Placebo	Cilostazol, 100 mg, Twice Daily	Cilostazol, 50 mg, Twice Daily	Placebo
	<b>Pain-Free Walking Distance</b>							
Baseline	...	...	...	...	...	70.4 (140)	66.5 (139)	72.4 (140)
4	1.12	1.15	1.05	.003	.003	85.7 (131)	80.1 (135)	75.4 (132)
8	1.31	1.26	1.14	.002	.009	100.3 (134)	90.0 (136)	90.0 (135)
16	1.43	1.42	1.15	<.001	<.001	112.4 (134)	103.0 (136)	91.9 (135)
20	1.49	1.44	1.20	.002	.002	127.1 (134)	111.1 (136)	95.1 (135)
24	1.59	1.48	1.20	<.001	<.001	137.9 (140)	115.1 (139)	95.5 (140)
<b>Maximal Walking Distance</b>								
Baseline	...	...	...	...	...	129.7 (140)	131.5 (139)	147.8 (140)
4	1.14	1.12	1.02	<.001	<.001	153.4 (131)	148.0 (135)	142.1 (132)
8	1.34	1.26	1.09	<.001	<.001	186.2 (134)	170.2 (136)	157.5 (135)
16	1.41	1.35	1.11	<.001	<.001	216.0 (134)	183.7 (136)	161.9 (135)
20	1.49	1.35	1.14	<.001	<.001	243.0 (134)	186.8 (136)	164.7 (135)
24	1.51	1.38	1.15	<.001	<.001	258.8 (140)	198.8 (139)	174.6 (140)



**Figure 2.** Geometric mean percent change in pain-free walking distance over time in the efficacy intent-to-treat population using last observation carried forward.



**Figure 3.** Geometric mean percent change in maximal walking distance over time in the efficacy intent-to-treat population using last observation carried forward.

cebo ( $P < .05$ ). Most headaches were mild or moderate and occurred during the first 2 weeks of therapy. Six patients discontinued use of study medication because of persistent or severe headache: 4 in the cilostazol, 100 mg, group and 2 in the cilostazol, 50 mg, group. Of the 28 patients who experienced palpitations, most reported them to be mild. Twenty-four (86%) of the 28 patients who reported palpitations had a history of hypertension, cardiac disease, or both. Seven patients withdrew from the study because of palpitation: 4 in the cilostazol, 100 mg, group and 3 in the cilostazol, 50 mg, group. Most cases of abnormal stool samples and diarrhea were mild to moderate. One patient with a history of gastrointestinal problems had continuous, severe diarrhea and withdrew from the study.

Significant positive changes were observed in high-density lipoprotein cholesterol and triglyceride levels in patients receiving cilostazol compared with those receiving

placebo. The least-squares mean of high-density lipoprotein increased 0.16 (6.3 mg/dL), 0.09 (3.5 mg/dL), and 0.04 mmol/L (1.7 mg/dL) after 24 weeks of treatment for the 100-mg, 50-mg, and placebo groups, respectively ( $P < .001$  for 100 mg vs placebo;  $P = .18$  for 50 mg vs placebo). All 3 treatment groups showed a trend toward reduced triglyceride and low-density lipoprotein cholesterol levels during the study, but greater and more immediate reductions in triglyceride level were observed in the 2 cilostazol groups. Compared with placebo, the least-squares mean change from baseline for triglyceride level was  $-1.09$ ,  $-0.82$ , and  $-0.50$  mmol/L ( $-96.9$ ,  $-72.3$ , and  $-44.0$  mg/dL) for the 100-mg, 50-mg, and placebo treatment groups, respectively ( $P < .001$  for 100 mg vs placebo;  $P = .046$  for 50 mg vs placebo). There was a trend toward reduction in total cholesterol level in patients receiving cilostazol. No other clinically relevant laboratory changes were seen.

**Table 4. Results of the Functional Status Questionnaires at Week 24 for All Patients With at Least One Data Point\***

Scale (Range)	Mean Score (Mean Change From Baseline)			3-Way Comparison P Values†
	Cilostazol, 100 mg, Twice Daily (n = 137)	Cilostazol, 50 mg, Twice Daily (n = 135)	Placebo (n = 141)	
<b>Medical Outcomes Scale Short Form-36 Questionnaire</b>				
Physical health (0-100)				
Physical function	61.6 (7.1)	59.3 (8.0)	53.8 (2.0)	.02
Role-physical	61.3 (5.3)	57.6 (4.4)	49.8 (-2.8)	.13
Bodily pain	62.9 (7.2)	58.4 (4.6)	54.0 (-1.8)	.002
Mental health (0-100)				
Social function	86.3 (1.0)	85.2 (0.9)	82.5 (0.4)	.93
Role-emotional	91.7 (2.9)	90.1 (0.0)	84.2 (-1.66)	.29
Mental health	82.2 (2.5)	80.3 (-1.5)	79.6 (0.9)	.03
<b>Walking Impairment Questionnaire</b>				
Walking speed (0-1)	0.56 (0.1)‡	0.50 (0.2)	0.44 (0.1)	.002
Walking distance (0-1)	0.53 (0.2)	0.47 (0.2)	0.38 (0.1)	.01
<b>Claudication Outcome Measures</b>				
Change in pain/discomfort (0-4)	... (2.8)	... (2.7)	... (2.4)	<.001
Pain/discomfort daily activities (0-4)	2.8 (0.4)	2.8 (0.5)	2.5 (0.2)	.07
Pain/discomfort physical activities (0-4)	2.5 (0.5)	2.3 (0.5)	2.1 (0.2)	<.001
Pain/discomfort social activities (0-4)	3.5 (0.3)	3.4 (0.4)	3.2 (0.3)	.85
Walking pain/discomfort (0-4)	2.4 (0.7)	2.1 (0.7)	1.8 (0.4)	.005
Worry/concern due to pain (0-4)	3.0 (0.8)	2.8 (0.6)	2.6 (0.5)	.05

\*For all scales, a higher score is indicative of better functioning. Ellipses indicate data not applicable.

†Three-way comparison based on the Kruskal-Wallis test on change from baseline. Pairwise comparisons based on the Wilcoxon rank sum test on change from baseline.

‡n = 136.

**Table 5. Global Therapeutic Assessment by Patient and Investigator at Week 24**

Judgment	Cilostazol, 100 mg, Twice Daily (n = 171), No. (%)	Cilostazol, 50 mg, Twice Daily (n = 170), No. (%)	Placebo (n = 169), No. (%)	3-Way Comparison P Value*
By investigator				
Much better	25 (14)	20 (12)	12 (7)	.03
Better	58 (33)	55 (32)	44 (26)	
Unchanged	80 (46)	86 (50)	99 (58)	
Worse	2 (1)	3 (2)	10 (6)	
Much worse	0 (0)	1 (1)	2 (1)	
Unknown	6 (3)	5 (3)	2 (1)	
By patient				
Much better	31 (18)	28 (16)	23 (14)	.002
Better	60 (34)	64 (37)	40 (24)	
Unchanged	69 (39)	70 (41)	84 (49)	
Worse	3 (2)	5 (3)	15 (9)	
Much worse	0 (0)	2 (1)	3 (2)	
Unknown	8 (5)	1 (1)	4 (2)	

\*Based on Cochran-Mantel-Haenszel test.

A dose-dependent increase in heart rate was observed for patients receiving cilostazol. Mean change from baseline in apical pulse at week 24 was 7.2/min, 3.7/min, and 0.2/min for the cilostazol, 100 mg, cilostazol, 50 mg, and placebo groups, respectively. Blood pressure remained stable during the study, with a slight trend toward a dose-dependent decrease in blood pressure in both cilostazol groups compared with the placebo group. No relevant findings were observed in the other assessed safety parameters.

**COMMENT**

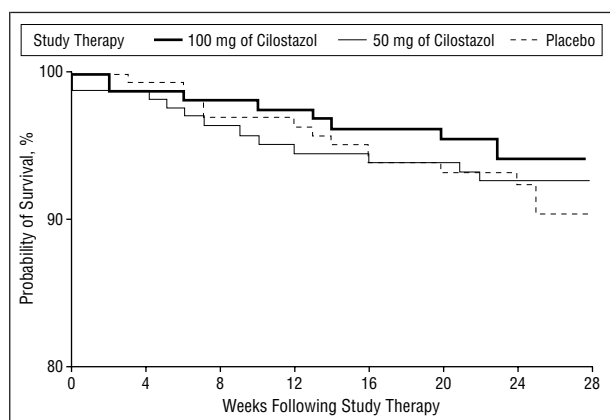
Patients with intermittent claudication as their only manifestation of lower extremity arterial occlusive disease do not have limb-threatening ischemia, and have several options for symptomatic relief. Percutaneous transluminal angioplasty and arterial bypass are costly, may be associated with significant morbidity or mortality, and should therefore be generally reserved for treatment of severe, incapacitating claudication.<sup>4</sup> Patients with mild-to-

**Table 6. Incidence of Deaths or Cardiovascular Events as Adjudicated by the Executive Committee**

Event	All Randomized Patients			
	Cilostazol, 100 mg, Twice Daily (n = 175), No. (%)	Cilostazol, 50 mg, Twice Daily (n = 171), No. (%)	Placebo (n = 170), No. (%)	Total (n = 516), No. (%)
Myocardial infarction	2 (1.1)	4 (2.3)	2 (1.2)	8 (1.6)
Stroke	3 (1.7)	2 (1.2)	2 (1.2)	7 (1.4)
Arterial revascularization* CABG/carotid endarterectomy/renal procedure	0 (0)	0 (0)	1 (0.6)	1 (0.2)
Peripheral vascular procedure/lower extremity bypass	2 (1.1)	5 (2.9)	5 (2.9)	12 (2.3)
Amputation	0 (0)	0 (0)	1 (0.6)	1 (0.2)
Death†	2 (1.1)	1 (0.6)	2 (1.2)	5 (1.0)

\*At the second meeting, executive committee members decided that arterial revascularization should be separated into categories: peripheral vascular disease procedures, which included lower extremity bypasses, and other procedures, which included coronary artery bypass grafts (CABGs), carotid endarterectomies, and renal procedures.

†All 7 patients who died are represented in this tabulation. The executive committee classified 2 deaths as stroke and myocardial infarction.



**Figure 4.** Probability of survival without cardiovascular morbidity and all-cause mortality events by treatment group.

moderate intermittent claudication should first be managed more conservatively by modifying risk factors such as smoking, sedentary lifestyle, and diet, which can improve overall cardiovascular risk.<sup>10</sup> However, patients who stop smoking and increase their walking exercise may see only a modest improvement in walking ability, and they must then adapt their lifestyle to a residual disability. Such patients might benefit from a medication that could produce even a limited improvement in walking ability.

Cilostazol has a number of physiological effects that may contribute to symptom relief in patients with intermittent claudication. Cilostazol inhibits platelet aggregation in a dose-dependent manner in the presence or absence of endothelial cells, although their presence potentiates this inhibitory effect.<sup>11,12</sup> In a small, double-blind, crossover study,<sup>13</sup> cilostazol inhibited thromboxane-stimulated platelet aggregation more effectively than aspirin or ticlopidine hydrochloride. The inhibition of primary and secondary platelet aggregation by cilostazol may have relevance to claudication through reduction in inflammatory cytokines stimulated by the ischemia reperfusion cycle of exercising muscle with a restricted blood supply.<sup>14</sup> Patients with intermittent clau-

**Table 7. Most Commonly Reported Potentially Drug-Related Treatment-Emergent Adverse Events by 10% or Greater Incidence in Any Treatment Group**

Adverse Event	All Randomized Patients			
	Cilostazol, 100 mg, Twice Daily (n = 175), No. (%)	Cilostazol, 50 mg, Twice Daily (n = 171), No. (%)	Placebo (n = 170), No. (%)	Total (n = 516), No. (%)
Headache*	60 (34.3)	40 (23.4)	25 (14.7)	125 (24.2)
Abnormal stool samples*	26 (14.9)	25 (14.6)	6 (3.5)	57 (11.0)
Diarrhea*	21 (12.0)	17 (9.9)	7 (4.1)	45 (8.7)
Dizziness	18 (10.3)	15 (8.8)	8 (4.7)	41 (7.9)
Palpitations*	20 (11.4)	8 (4.7)	0 (0)	28 (5.4)

\*P<.05.

dication also have impaired fibrinolysis associated with elevated plasminogen activator inhibitor.<sup>15</sup> Experimentally, the phosphodiesterase inhibitor HL 725 has been observed to decrease plasminogen activator inhibitor messenger RNA levels.<sup>16</sup> However, this clinical trial did not attempt to assess whether such effects occurred. Cilostazol produces mild vasodilation by direct action on vascular smooth muscle by increasing intracellular cyclic adenosine monophosphate. This effect blocks the release of calcium ions from intracellular storage granules, inhibiting contractile protein function.<sup>17</sup> Nonspecific vasodilatory effects such as palpitation or slight heart rate increase were observed in this study, but the significance of this in terms of claudication symptom relief is unknown. Cilostazol also inhibits replication and growth of rat vascular smooth muscle cells in tissue culture.<sup>18</sup>

Cilostazol was approved by the Ministry of Health and Welfare in Japan in 1988 for the treatment of intermittent claudication, and approximately 725 000 patients have been treated with cilostazol in Japan since 1988. Pentoxifylline, which was approved by the Food and Drug Administration in 1984, was introduced in Eu-

## Investigators

J. Michael Bacharach, MD, and Robert A. Graor, MD, *Cleveland Clinic Foundation, Cleveland, Ohio*; Hugh G. Beebe, MD, *Jobst Vascular Center, Toledo, Ohio*; Dennis G. Caralis, MD, *Rush-Presbyterian Hospital, Chicago, Ill*; John Castronuovo, MD, *Morristown Memorial Hospital, Morristown, NJ*; Anthony Comerota, MD, *Temple University Hospital, Philadelphia, Pa*; Philip Comp, MD, *University of Oklahoma Health Sciences Center, Oklahoma City*; John Corson, MD, *University of Iowa Department of Surgery, Iowa City*; Jack Cronenwett, MD, *Dartmouth Hitchcock Medical Center, Lebanon, NH*; Robin Crouse, MD, *Bowman Gray School of Medicine, Winston-Salem, NC*; Bruce Cutler, MD, *University of Massachusetts Medical Center, Worcester*; Ron Dalman, MD, *V.A. Medical Center Department of Vascular Surgery, Palo Alto, Calif*; Michael Dalsing, MD, *Wishard Hospital, Indiana University, Indianapolis*; David L. Dawson, MD, *Wilford Hall Medical Center, Lackland Air Force Base, San Antonio, Tex*; Robert Fried, MD, *Paoli Memorial Hospital, Paoli, Pa*; Roger Gregory, MD, *Norfolk Surgical Group, Norfolk, Va*; Sushil Gupta, MD, *MetroWest Medical Center, Framingham, Mass*; J. Alan Herd, MD, *The Methodist Hospital, Houston, Tex*; Glenn Hunter, MD, *University of Arizona Health Sciences Center, Tucson*; Michael Jaff, DO, and Gerald Dorros, MD, *Dorros-Feurer Foundation, Milwaukee, Wis*; Richard Kempczinski, MD, *University of Cincinnati Medical Center, Cincinnati, Ohio*; Tom Kerr, MD, *Bay Pines Medical Center, Bay Pines, Fla*; John B. Kostis, MD, *UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ*; Parry B. Larsen, MD, *Miami Heart Institute, Miami Beach, Fla*; Michael Lilly, MD, *University of Maryland at Baltimore*; Walt McCarthy, MD, *Northwestern University Medical School, Chicago, Ill*; James O. Menzoian, MD, *Boston University Medical Center, Boston, Mass*; T.A. Don Michael, MD, and Brijesh Bhambi, MD, *Central Cardiology Medical Clinic, Bakersfield, Calif*; Barry L. Molk, MD, *Aurora Denver Cardiology Association, Aurora, Colo*; Samuel Money, MD, *Ochsner Medical Foundation, New Orleans, La*; Steve Panian, MD, *St. Joseph Hospital Research Department, Denver, Colo*; Jacob Robison, MD, *Medical University of South Carolina, Charleston*; David Sheps, MD, *University of North Carolina, Chapel Hill*; Anton Sidawy, MD, *Chief of Vascular Surgery, Surgical Service 112 VA Medical Center, Washington DC*; Geza Simon, MD, *Hypertension Clinic VA Medical Center, Minneapolis, Minn*; James Smith, DO, *Galichia Medical Group, Wichita, Kan*; Eugene Strandness, MD, *University of Washington Hospital, Seattle*; and Albert Yellin, MD, *LAC and USC School of Medicine, Los Angeles, Calif*.

rope more than 20 years ago and remains an agent widely used for the treatment of intermittent claudication in the United States. Its mechanism of action differs distinctly from that of cilostazol. Pentoxifylline is a xanthine derivative possessing rheologic properties that improve red blood cell flexibility, reducing blood viscosity and increasing muscular blood flow.<sup>19</sup> Clinical studies<sup>20,21</sup> have shown that pentoxifylline improves both pain-free and maximal walking distances in patients with intermittent claudication. In a large double-blind study, pentoxifylline improved pain-free walking distance by 59% after 24 weeks of treatment ( $P = .11$ ) compared with placebo.

The mean change in maximal walking distance in the pentoxifylline group was 38% ( $P = .19$ ) compared with placebo.<sup>20</sup> However, the clinical benefit of pentoxifylline has been questioned.<sup>22</sup> Newer vasodilators such as nafronyl oxalate<sup>23</sup> and buflomedil<sup>24</sup> have also demonstrated improvement in pain-free walking distance. Platelet aggregation inhibitors such as ticlopidine<sup>25,26</sup> and metabolic agents such as L-carnitine<sup>27</sup> have also shown some promise in improving walking ability in patients with intermittent claudication.

Patients in this trial were assessed by constant-load treadmill testing at a 12.5% grade and a speed of 3.2 km/h. Criticisms of this method, as opposed to graded treadmill testing, include observations supporting the "learning curve" placebo effect,<sup>28</sup> the problem of using a single stress level for a population with a heterogeneous walking ability, and the likelihood that constant-load testing may underestimate the therapeutic effects of a study medication.<sup>29</sup> Despite this possibility, we showed a clear benefit with cilostazol. We chose to use constant-load treadmill testing because it is well accepted by patients and, more importantly, it provides a consistent comparison with the existing literature for more than 2 decades.

The results of this study showed that cilostazol produces a dose-dependent improvement in treadmill walking distance in patients with intermittent claudication, which progressively increased during the 24 weeks of treatment. At week 24, patients who received cilostazol, 100 mg, twice a day increased their ability to walk without stopping by 129.1 m compared with baseline. Patients who received cilostazol, 50 mg, walked 67.3 m more without stopping compared with baseline. These results are clinically and statistically superior to the 26.8 m increase in maximal walking distance seen in the placebo group. Minor adverse effects were fairly common but usually self-limited and caused only a few patients to ask to discontinue use of the medication.

Cilostazol, 100 mg or 50 mg, twice a day was consistently more effective than placebo in improving walking distances, suggesting that this medication may be a useful new tool in the management of intermittent claudication.

Accepted for publication January 25, 1999.

This study was sponsored in part by Otsuka America Pharmaceutical Inc, Rockville, Md.

We gratefully acknowledge Jacqueline Stedman, MPH, Jobst Vascular Center, for preparation and revision of this manuscript.

Reprints: Hugh G. Beebe, MD, Jobst Vascular Center, 2109 Hughes Dr, Toledo, OH 43606 (e-mail: hbeebe@jvc.org).

## REFERENCES

1. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation*. 1985; 71:510-515.
2. Vogt MT, Wolfson SK, Kuller LH. Lower extremity arterial disease and the aging process: a review. *J Clin Epidemiol*. 1992;45:529-542.
3. Hertzner NR. The natural history of peripheral vascular disease: implications for its management. *Circulation*. 1991;83(suppl 1):112-119.

4. Pentecost MJ, Criqui MH, Dorros G, et al. Guidelines for peripheral percutaneous transluminal angioplasty of the abdominal aorta and lower extremity vessels. *Circulation*. 1994;89:511-531.
5. Okuda Y, Kimura Y, Yamashita K. Cilostazol. *Cardiovasc Drug Rev*. 1993;11:451-465.
6. Ware JE Jr. *SF-36 Health Survey: Manual and Interpretation Guide*. Boston, Mass: The Health Institute, New England Medical Center; 1993.
7. Regensteiner JG, Steiner JF, Panzer RJ, Hiatt WR. Evaluation of walking impairment by questionnaire in patients with peripheral arterial disease. *J Vasc Med Biol*. 1990;2:142-152.
8. Fisher LD, Van Belle G. *Biostatistics: A Methodology for the Health Sciences*. New York, NY: John Wiley & Sons; 1993:307, 315-319, 430-432. Wiley Series in Probability and Mathematical Statistics.
9. Fleiss JL. *The Design and Analysis of Clinical Experiments*. New York, NY: John Wiley & Sons; 1986:155-159. Wiley Series in Probability and Mathematical Statistics.
10. Straznicki NE, Louis WJ, McGrade P, Howes LG. The effects of dietary lipid modification on blood pressure, cardiovascular reactivity and sympathetic activity in man. *J Hypertens*. 1993;11:427-437.
11. Igawa T, Tani T, Chijiwa T, et al. Potentiation of anti-platelet aggregating activity of cilostazol with vascular endothelial cells. *Thromb Res*. 1990;57:617-623.
12. Kimura Y, Tani T, Kanbe T, Watanabe K. Effect of cilostazol on platelet aggregation and experimental thrombosis. *Arzneimittelforschung*. 1985;35:1144-1149.
13. Ikeda Y, Kikuchi M, Murakami H, et al. Comparison of the inhibitory effects of cilostazol, acetylsalicylic acid and ticlopidine on platelet functions ex vivo: randomized, double-blind crossover study. *Arzneimittelforschung*. 1987;37:563-566.
14. Tsang GMK, Sanghera K, Gosling P, et al. Pharmacological reduction of the systemically damaging effects of local ischaemia. *Eur J Vasc Surg*. 1994;8:205-208.
15. Killewich LA, Gardner AW, Macko RF, et al. Progressive intermittent claudication is associated with impaired fibrinolysis. *J Vasc Surg*. 1998;27:645-650.
16. Konkle BA, Kollros PR, Kelly MD. Heparin-binding growth factor-1 modulation of plasminogen activator inhibitor-1 expression: interaction with cAMP and protein kinase C-mediated pathways. *J Biol Chem*. 1990;265:21867-21873.
17. Tanaka T, Ishikawa T, Hagiwara M, Onoda K, Itoh H, Hidaka H. Effects of cilostazol, a selective cAMP phosphodiesterase inhibitor on the contraction of vascular smooth muscle. *Pharmacology*. 1988;36:313-320.
18. Takahashi S, Oida K, Fujiwara R, et al. Effect of cilostazol, a cyclic AMP phosphodiesterase inhibitor, on the proliferation of rat aortic smooth muscle cells in culture. *J Cardiovasc Pharmacol*. 1992;20:900-906.
19. Aviado DM, Porter JM. Pentoxifylline: a new drug for the treatment of intermittent claudication: mechanism of action, pharmacokinetics, clinical efficacy and adverse effects. *Pharmacotherapy*. 1984;4:297-307.
20. Porter JM, Cutler BS, Lee BY, et al. Pentoxifylline efficacy in the treatment of intermittent claudication: multicenter controlled double-blind trial with objective assessment of chronic occlusive arterial disease patients. *Am Heart J*. 1982;104:66-72.
21. Reich T, Gillings D. Effects of pentoxifylline on severe intermittent claudication. *Angiology*. 1987;38:651-656.
22. Green RM, McNamara J. The effects of pentoxifylline on patients with intermittent claudication. *J Vasc Surg*. 1988;7:356-362.
23. Trubestein G, Bohme H, Heidrich H, et al. Naftidrofuryl in chronic arterial disease: results of a controlled multicenter study. *Angiology*. 1984;35:701-708.
24. Trubestein G, Balzer K, Bisler H, et al. Buflomedil in arterial occlusive disease: results of a controlled multicenter study. *Angiology*. 1984;35:500-505.
25. Balsano F, Coccheri S, Libretti A, et al. Ticlopidine in the treatment of intermittent claudication: a 21-month double-blind trial. *J Lab Clin Med*. 1989;114:84-91.
26. Arcan JC, Blanchard J, Boissel JP, Destors JM, Panak E. Multicenter double-blind study of ticlopidine in the treatment of intermittent claudication and the prevention of its complications. *Angiology*. 1988;39:802-811.
27. Brevetti G, Chiariello M, Ferulano G, et al. Increases in walking distance in patients with peripheral vascular disease treated with L-carnitine: a double-blind, cross-over study. *Circulation*. 1988;77:767-773.
28. Skinner JS, Strandness DE Jr. Exercise and intermittent claudication. I: effect of repetition and intensity of exercise. *Circulation*. 1967;36:15-22.
29. Hiatt WR, Hirsch AT, Regensteiner JG, Brass EP. Clinical trials for claudication: assessment of exercise performance, functional status, and clinical end points. *Circulation*. 1995;92:614-621.