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Treatment of Intermittent Claudication With Beraprost Sodium, an Orally Active Prostaglandin I_2 Analogue

A Double-Blinded, Randomized, Controlled Trial

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OBJECTIVES In the current study, we hypothesized that beraprost would: 1) improve treadmill exercise performance and quality of life; and 2) decrease rates of ischemic events in patients with intermittent claudication.

BACKGROUND Previous trials with beraprost sodium, an orally active prostaglandin I_2 analogue, in the treatment of claudication in patients with peripheral arterial disease (PAD) have been inconsistent.

METHODS Patients with intermittent claudication (n = 897) were randomized to receive either 40 μg three times a day of beraprost with meals (n = 385) or placebo (n = 377) in a double-blinded manner for one year. The primary efficacy parameter was treadmill-measured maximum walking distance, as assessed at three and six months after randomization. Secondary efficacy parameters included treadmill-measured pain-free walking distance and change in quality of life.

RESULTS There was no significant improvement in maximum walking distance in the beraprost group (16.7%) as compared with the placebo group (14.6%, p = NS). Administration of beraprost did not improve the pain-free walking distance (p = NS between treatment groups), and there was no improvement in the quality-of-life measures between the treatment groups. The incidence of critical cardiovascular events was 7.3% in the beraprost group and 11.4% in the placebo group (p = NS). There was a significant reduction in the combination of cardiovascular death and myocardial infarction in the beraprost group (p = 0.01).

CONCLUSIONS Despite previous investigations suggesting efficacy, these results indicate that beraprost is not an effective treatment to improve symptoms of intermittent claudication in patients with PAD. The potential benefit of beraprost on critical cardiovascular events would require confirmation in a larger prospective investigation. (J Am Coll Cardiol 2003;41:1679–86)

Peripheral arterial disease (PAD) is a common condition in the U.S., with an estimated prevalence of 12% in the general population; PAD has been estimated to affect ~8 million Americans (1). It is also common in primary care office practices and is present in 29% of patients >70 years of age

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or >50 years of age with a history of smoking or diabetes (2). In this office-based population, up to 24% of subjects may suffer claudication symptoms, as defined by their physicians (2). These claudication symptoms are associated with a marked impairment in quality of life (QOL).

Improvement of claudication symptoms can be accomplished by prescription of supervised exercise rehabilitation (Anonymous, Current Procedural Terminology [CPT], 2001. Unpublished data) (3), use of claudication pharmacotherapies (4,5), or selective use of revascularization strategies (6). There are currently two medications approved by the U.S. Food and Drug Administration (FDA) approved for the relief of claudication: pentoxifylline (Trental) and cilostazol (Pletal) (7). Whereas pentoxifylline has demonstrated limited therapeutic efficacy, cilostazol has consistently been shown in multiple prospective clinical trials to improve exercise performance and QOL in patients with claudication (8–10). It is notable that neither medication has been prospectively evaluated for its ability to decrease cardiovascular ischemic events. Despite current therapeutic choices to treat claudication, there remain many patients who do not respond adequately to current pharmacotherapies, who may not be amenable to participation in exercise programs, or whose limb arterial anatomy or procedural risk/benefit ratio is unfavorable for revascularization. Thus, a large population of patients with claudication would benefit from the availability of additional orally active therapeutic agents that could further diminish claudication symptoms and whose pharmacologic profile might decrease cardiovascular event rates.

Prostaglandin I_2 (PGI_2), or prostacyclin, is produced by endothelial cells and has such a promising pharmacologic

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Abbreviations and Acronyms

ABI = ankle-brachial index
BERCI-2 = Beraprost et Claudication Intermittente study
MWD = maximum walking distance
PAD = peripheral arterial disease
PFWD = pain-free walking distance
PGI_2 = prostaglandin I_2
QOL = quality of life
SF-36 = short-form 36
TID = three times a day
WIQ = walking impairment questionnaire

profile. This naturally occurring prostanoid relaxes vascular smooth muscle (11,12), inhibits platelet aggregation (11,12), and also suppresses vascular smooth muscle proliferation (13). Beraprost sodium is an orally active PGI_2 analogue that elicits vasodilating and antiplatelet properties in vivo (14,15).

The Beraprost et Claudication Intermittente study (BERCI-2) (16) demonstrated that both maximum walking distance (MWD) and pain-free walking distance (PFWD) were increased significantly in patients receiving beraprost sodium. However, another trial of beraprost that evaluated 330 patients with claudication showed no significant improvement in MWD (17). These inconsistent trial efficacy outcomes led to the design of the current investigation. We hypothesized that treatment with beraprost would improve measures of walking distance and community-based functional status.

METHODS

Trial design. The current investigation was a randomized, double-blinded, multicenter, placebo-controlled trial conducted at sites in the U.S. Patients underwent a single-blinded, placebo run-in phase after which they were randomly assigned to receive 40 μg three times a day (TID) of beraprost with meals or placebo for one year. Although the primary efficacy end point was treadmill walking distance after six months of treatment, the treatment was continued for one year to assess safety. The protocol was approved by the ethical committees of the respective institutions participating in the study, and each patient offered written, informed consent.

Outcomes. The primary claudication efficacy outcome of the trial was MWD on a treadmill at 24 weeks. Maximum walking distance (recorded in feet) was defined as the distance walked until the patient was forced to stop from maximum claudication pain. The principal reinforcing outcome measure was the change in PFWD, defined as the distance walked before the onset of pain. The secondary end points included subjective walking distance, as assessed by the Walking Impairment Questionnaire (WIQ), a health-related QOL questionnaire (short-form 36 [SF-36]), a change in the ankle-brachial index (ABI), and the incidence of critical cardiovascular events, as defined subsequently. A "responder profile" was defined "pre hoc" as any patient with a >35% increase in the treadmill-derived PFWD, compared with baseline (day of randomization), at six months, and in the absence of critical cardiovascular events, and was considered a secondary outcome.

Quality of life was assessed using previously validated questionnaires, the SF-36, and the WIQ measured at run-in day 14 (baseline) and weeks 12 and 24 (18). Critical cardiovascular events were defined as death of cardiovascular origin (confirmed or sudden death), nonfatal myocardial infarction, or unstable angina; stroke or transient ischemic attack; and critical leg ischemia (rest pain necessitating urgent medical intervention or a surgical procedure to avoid amputation), subacute critical ischemia (continuous rest pain for >2 weeks requiring analgesics), peripheral angioplasty, peripheral bypass surgery, or amputation at any level. All critical cardiovascular events were adjudicated by an independent Critical Cardiovascular Events Committee.

Patient selection. Patients were included if they were between 40 and 80 years of age, with stable, intermittent claudication for longer than six months. They were also required to have a rest ABI ≤0.90, with a 10 mm Hg decrease in ankle pressure 1 min after completing the exercise treadmill test; PFWD on a standardized treadmill test ≥164 feet (50 m) but ≤984 feet (300 m) at the screening visit; and PFWD variability <25% between the tests performed during the run-in phase.

Patients were excluded from the study if they had critical limb ischemia (defined as the presence of rest pain requiring analgesics >2 weeks or the presence of lower limb ulcers or gangrene); underwent coronary artery or peripheral artery angioplasty or surgical limb arterial bypass within the last three months; were anticipated to require surgical or percutaneous revascularization within six months of randomization; or were currently participating in a supervised exercise regimen. Exclusion was also mandated for patients who had a stroke or myocardial infarction or deep-vein thrombosis within the last three months; nonatherosclerotic PAD (e.g., thromboangiitis obliterans); a known abdominal aortic aneurysm ≥4.5 cm; unstable angina pectoris within the last three months; heart failure (New York Heart Association functional class III or IV); severe, uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >95 mm Hg); anemia (hemoglobin <10 g/dl in women and 11 g/dl in men) or any clinically significant bleeding episode within the last year; an abnormal platelet count (platelets >150,000 mm^3 or <60,000/mm^3). Additional exclusion criteria included type I diabetes mellitus; morbid obesity (body mass index >40 kg/m^2); severe renal insufficiency (creatinine >2.5 mg/dl); severe hepatic insufficiency (alanine transaminase and aspartate transaminase ≥3 times the upper normal limit on two separate tests); any disorder that would affect the interpretation of treadmill test results; and any other life-threatening disease or any psychiatric condition that would impair either informed consent or compliance with the

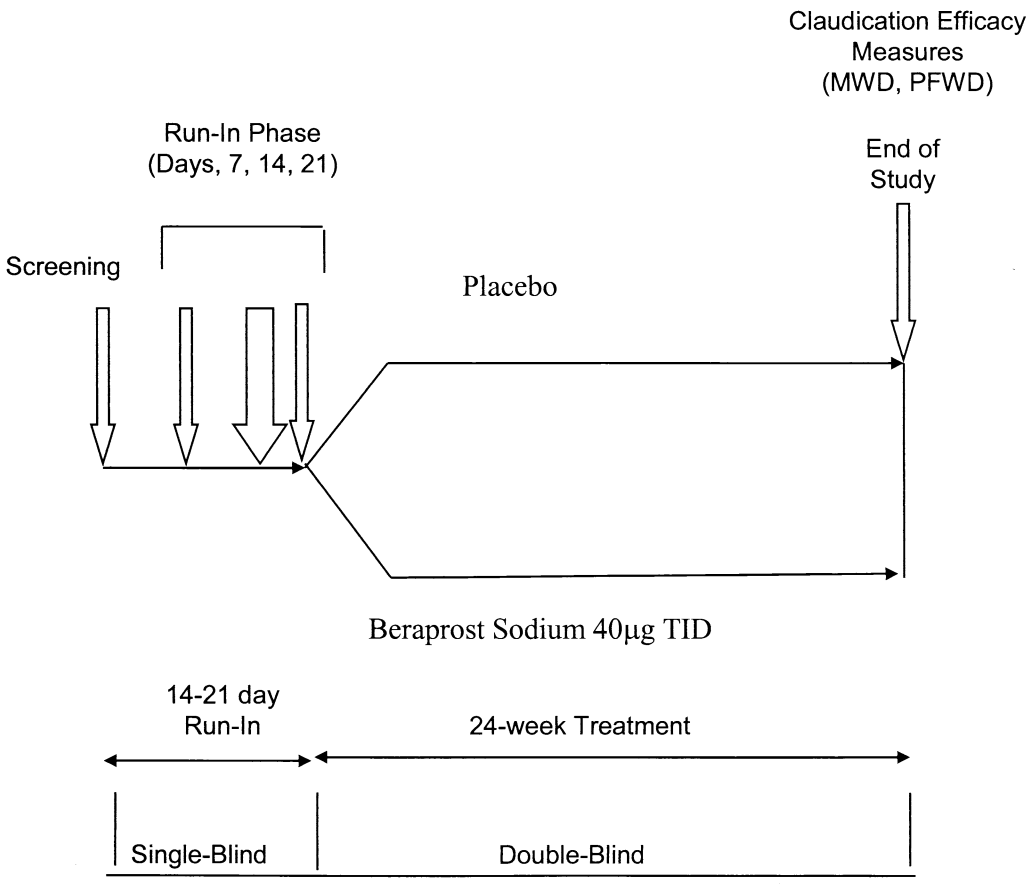

Figure 1. Study design for this trial. The current study was prospective, randomized, and placebo-controlled, with identical outcome measures and treadmill protocol as in the previously published BERCI-2 study (16). MWD = maximum walking distance; PFWD = pain-free walking distance; TID = three times a day.

study protocol. Additional exclusion criteria included use of cilostazol, pentoxifylline, or HeartBar (L-arginine) within one month prior to the screening treadmill test; current use of warfarin, heparin, or thrombolytic therapy; or any disease state that could potentially decrease gastrointestinal absorption of the study medication. Patients using aspirin, clopidogrel, or ticlopidine were *not* excluded from the study.

Study screening and procedures. The study protocol is outlined in Figure 1. After provision of informed consent, all patients underwent a full medical history, as well as assessment of current lifestyle and atherosclerosis risk factors. The clinical examination included a full physical examination, 12-lead electrocardiogram, clinical laboratory tests, assessment of concomitant medications, and ABI measurement. Patients then underwent a screening exercise treadmill test, from which the PFWD and MWD were recorded. The treadmill protocol utilized a constant grade (10%) and speed from the onset of 1.9 mph (3 km/h). The test was timed in minutes and seconds, and the elapsed time was used to calculate the exact distance walked for PFWD and MWD. The PFWD needed to be ≥164 feet but ≤984 feet. If the patient met the treadmill walking and selection criteria, the placebo drug was dispensed and a single-blinded run-in phase was begun.

During the placebo run-in phase, patient compliance was assessed by a pill count, and compliance was mandated to remain within 75% to 125% to permit continuation in the protocol. Changes in any concomitant medications were noted, and a baseline exercise treadmill test was performed on day 7. Patients underwent another baseline exercise treadmill test on day 14 of the run-in phase and were eligible for randomization if the PFWD was within 25% between the day 7 and day 14 values and all other criteria were met. Patients who did not meet the claudication distance criteria for the study were given the opportunity to undergo a third baseline treadmill test on day 21 of the run-in phase. Subsequent efficacy exercise treadmill tests were then performed at weeks 6, 12, 18, and 24.

Statistical analysis. SAMPLE SIZE CONSIDERATIONS. The effect of beraprost on MWD at week 24, as measured on a fixed treadmill test, was the primary end point for this trial and was the basis on which the sample size was estimated. The results of the intention-to-treat analysis of treadmill exercise tests in 422 PAD patients who received beraprost for 24 weeks in a phase III study in Europe (BERCI-2) were used as the basis of sample size estimates. The treadmill test parameters and run-in phase PFWD inclusion criteria in BERCI-2 were identical to those in this trial. In

Table 1. Baseline Demographic Data by Treatment Group for Current Study and BERCI-2 Study

	Current Study		BERCI-2	
	Beraprost	**Placebo**	**Beraprost**	**Placebo**
Age (yrs)	65.9	65.7	63.3	61.5
Male	306 (79%)	279 (74%)	85%	84%
Duration of claudication (yrs)	6.4	6.6	6.4	5.3
Previous surgery	88 (23%)	92 (24%)	28%	26%
Hypertension	282 (73%)	284 (75%)	41%	43%
Diabetes	111 (29%)	111 (29%)	18%	18%
Smoker				
Current	127 (33%)	129 (34%)	34%	40%
Former	234 (61%)	217 (58%)	58%	51%
Dyslipidemia	270 (70%)	269 (71%)	43%	46%
ABI (before ETT)	0.64	0.65	0.73	0.71
MWD (feet)	538	560	901	888
PFWD (feet)	279	296	427	438

Data are presented as the mean value or number (%) of subjects. There was no difference between the treatment groups for either the current study or BERCI-2 study. There was a higher percentage of patients with diabetes, hypertension, and dyslipidemia in the current study, than in BERCI-2. The ABI, MWD, and PFWD were lower in the current study than in BERCI-2.

ABI = ankle-brachial index; ETT = exercise treadmill test; MWD = maximum walking distance; PFWD = pain-free walking distance.

BERCI-2, MWD increased by 65.8% for beraprost-treated patients and by 38.7% for placebo-treated patients at 24 weeks. This corresponds to a treatment difference in natural logarithms of *log* (165.8/138.7) = 0.179; its standard error of 0.048 corresponds to a standard deviation of ~0.5. Under the assumption of an effect size of 0.18, a slightly larger standard deviation of 0.54, an alpha level of 0.01, a two-sided comparison of the null hypothesis in which the mean values are equal, and a 95% power calculation, the sample size based on the normal distribution calculation was 323 patients per group ($n = [2.576 + 1.645]^2 \times 2 \times [0.542]/[0.182]$). Adjustment for using a nonparametric test (assuming normal distributions) brought the sample size to 344 patients per group.

Data analysis. The primary end point was MWD, which was not distributed normally and therefore was analyzed as log-transform values (log [value/baseline], where log use equals the natural algorithm). The results were thus presented as geometric mean values. Statistical significance was determined at $p < 0.05$. Data are presented as the mean value ± SEM. The incidence of the first cardiovascular or critical event was analyzed by the log-rank test.

RESULTS

Beginning in the year 2000, 882 patients entered into the three-week, single-blinded, run-in phase. Of these, 762 patients were randomized to receive beraprost or placebo in the double-blinded, one-year study. Reasons for nonrandomization included treadmill variability for PFWD >25% during the run-in phase (n = 37), withdrawal of consent (n = 26), abnormal laboratory results (n = 22), protocol violation (n = 20), occurrence of an adverse event (n = 12), compliance failure (n = 2), and loss to follow-up (n = 1). Thus, there were 385 patients in the beraprost group and 377 patients in the placebo group. The demographic data of patients by treatment assignment are listed in Table 1. The distribution of atherosclerosis risk factors, such as smoking, dyslipidemia, hypertension, and diabetes mellitus, were representative of patients with PAD and were not different between the two groups (p = NS for each comparison). Concomitant medications used by study patients included angiotensin-converting enzyme inhibitors, calcium channel blockers, nitrates, lipid-lowering drugs, oral antidiabetic agents, and diuretics. The use of concomitant medications, including aspirin (n = 249 for placebo and n = 244 for beraprost), clopidogrel (n = 21 for placebo and n = 27 for beraprost), and ticlopidine (n = 3 for placebo and n = 1 for beraprost), was not different between the treatment groups.

Study medication withdrawal rates and adverse event rates. Of the 762 patients who were randomized to receive study medication in the double-blinded phase of the study, a total of 113 patients (29%) discontinued treatment prematurely, primarily due to anticipated prostanoid adverse events (Table 2). Headache was more common in the patients treated with beraprost versus placebo (27.5% vs. 5.0%, $p < 0.001$). Vasodilation occurred more commonly in the beraprost group than in the placebo group (13.5% vs. 4%, $p < 0.001$). Diarrhea (7.3% vs. 1.3%), pain (5.5% vs. 1.1%), and nausea (4.4% vs. 1.3%) also occurred more frequently in the beraprost group than in the placebo group ($p < 0.02$ for all). The most common adverse events leading

Table 2. Reasons for Discontinuation of Study Medication

	Beraprost Group (n = 385)	**Placebo Group (n = 377)**
Died	1 (<1%)	1 (<1%)
Deterioration	13 (3%)	10 (3%)
Adverse events	57 (15%)	17 (5%)
Withdrew consent	25 (6%)	17 (5%)
Protocol violation	8 (2%)	5 (1%)
Lost to follow-up	9 (2%)	1 (<1%)
Total	113 (29%)	51 (14%)

Data are presented as the number (%) of subjects.

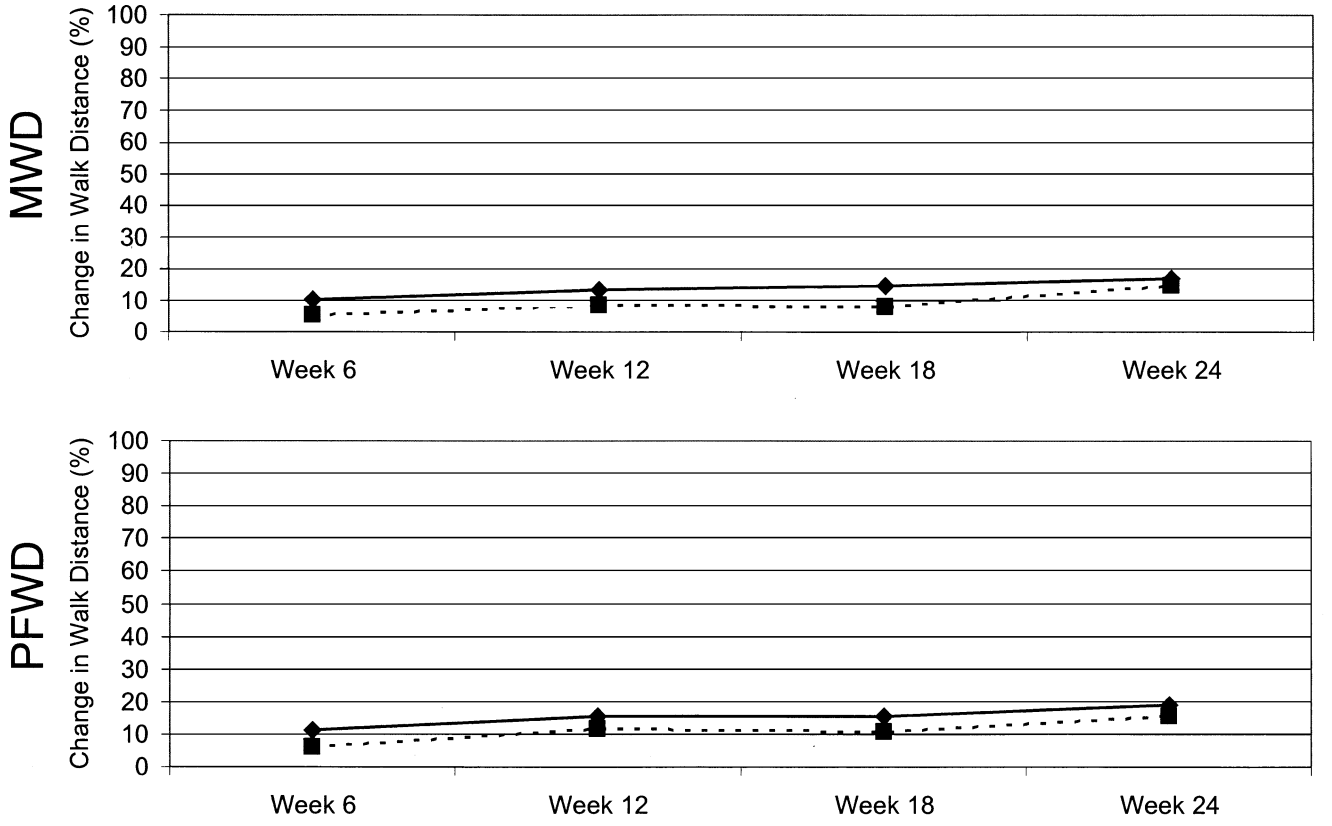

Figure 2. Graph showing maximum walking distance (MWD) **(top panel)** and pain-free maximum walking distance (PFWD) **(bottom panel)** for beraprost **(diamonds)** and placebo **(squares).** There was no significant difference in MWD and PFWD between beraprost and placebo.

to discontinuation included headache and vasodilation (8.6% and 3.9% in the beraprost group, respectively; $p < 0.001$ for both comparisons). There was no significant difference in serious adverse events and compliance with medication between the two groups.

Exercise treadmill results. There was no difference in the primary efficacy parameter of mean MWD at baseline and at week 24 between the treatment groups: 16.7% and 14.6% for beraprost and placebo, respectively (Fig. 2). Also, there was no significant change throughout the entire study for the primary reinforcing end point of mean PFWD at week 24 between the treatment groups: 19.2% and 15.4% for beraprost and placebo, respectively ($p = 0.24$) (Fig. 2). Figure 3 shows the percent change from baseline for MWD and PFWD between the two treatment groups ($p = NS$). When the data were analyzed according to a per-protocol population (those patients who completed the entire 24 weeks of the study), there was no difference in the primary and principal reinforcing end points between the two groups ($p = NS$). Evaluation for clinical responders, defined as a 35% increase in MWD in the absence of any clinical cardiovascular event, demonstrated no difference between the groups. The measured response rate was 31% in the active beraprost treatment group, compared with 33% in the placebo group ($p = 0.75$).

The ABI remained stable throughout the study and did not differ between the two groups. There was also no difference between the two groups regarding compliance with study drug or tobacco consumption. There was no interaction of the primary end point with other background variables, such as hypertension, diabetes, smoking, and dyslipidemia.

Quality-of-life outcomes. There was no significant difference in the QOL measures between the beraprost and placebo groups at week 24. Specifically, the WIQ distance and speed scores were unchanged from baseline to study conclusion for distance and speed ($p = NS$) in the beraprost group. Similarly, the baseline and final SF-36-derived physical component score was unchanged (47 vs. 50 and 50 vs. 51 for the beraprost and placebo groups, $p = NS$ for both comparisons). No differences in these QOL parameters were observed between the treatment groups.

Critical cardiovascular event rates. Critical cardiovascular events occurred in 28 patients treated with beraprost and 43 on placebo (Table 3). However, when the combination of cardiovascular death and myocardial infarction were counted separately, there were nine in the placebo group and one in the beraprost group ($p = 0.01$). This intriguing difference in a single ischemic end point (numbers of fatal and nonfatal myocardial infarctions between treatment groups) cannot serve as the basis for conclusions regarding the potential cardioprotective effect of beraprost, as the combined primary critical cardiovascular end point was not statistically different between the treatment cohorts.

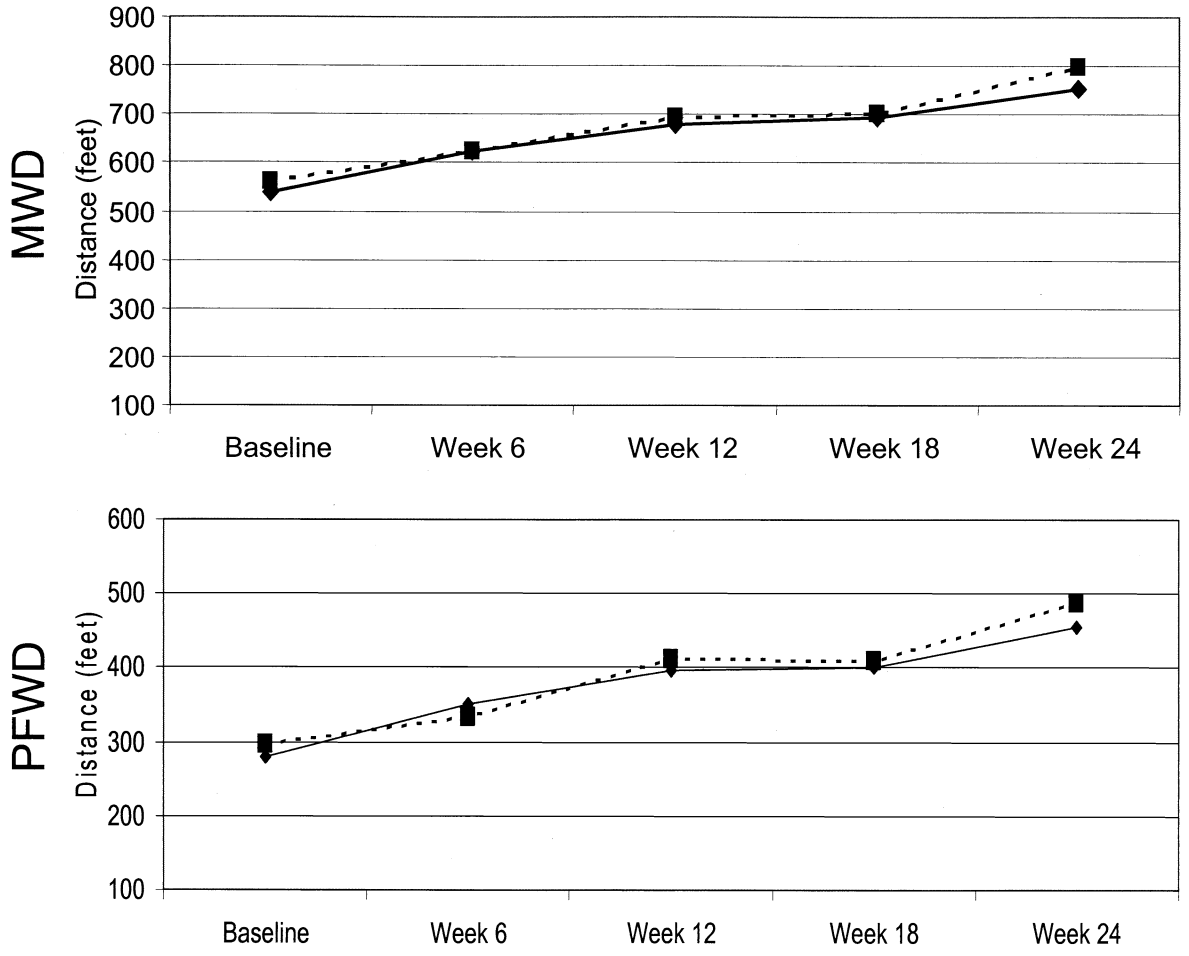

Figure 3. Graph showing percentage change from baseline in MWD **(top panel)** and PFWD **(bottom panel)** for beraprost **(diamonds)** and placebo **(squares)**. There was no significant difference in MWD and PFWD between beraprost and placebo. Abbreviations as in Figure 2.

DISCUSSION

Prolonged oral administration of the PGI_2 analogue beraprost over a period of six months did not improve any objective or subjective measure of claudication symptoms in this large, prospective trial. Specifically, MWD, PFWD, the responder profile, and patient-reported measures of walking impairment or QOL did not improve, compared with placebo, in patients with intermittent claudication. Although the current study demonstrated a nonsignificant decrease in critical cardiovascular events (including fatal and nonfatal systemic and limb events and revascularizations) in beraprost-treated patients, there was a significant reduction in the combination of cardiovascular death and myocardial infarction in those patients assigned to beraprost.

Table 3. Critical Cardiovascular Events in Intention-to-Treat Population

Event	Beraprost	Placebo
Cardiovascular death	1	4
Myocardial infarction	0	5
Unstable angina	5	7
Cardiovascular revascularization	7	7
Cerebrovascular accident	5	4
Worsening limb ischemia	6	8
Limb revascularization	4	8
Limb amputation	0	0
Total events	28	43

These results are similar to a previous study, also conducted in the U.S., of beraprost evaluated in 330 patients with claudication (17). In this previous study, patients were randomized to placebo or oral beraprost over a dose range of 30, 60, or 90 μg twice daily. After three months, there were no differences in MWD measured on a graded treadmill protocol or in MWD measured on a constant-load treadmill protocol. Thus, the total U.S. experience with beraprost in claudication in clinical trials totals over 1,100 patients. This trial and that one (17) have failed to provide any evidence of efficacy by measures of either treadmill exercise performance (using two different validated protocols) or disease-specific or general QOL.

The estimated half-life of this compound is ~45 min, with linear pharmacokinetic characteristics at doses ranging from 20 to 60 μg TID. The effect of beraprost on walking distance in patients with intermittent claudication was assessed in the BERCI dose-effect study (19). In this

double-blinded, randomized, multicenter, placebo-controlled trial, beraprost was shown to increase the PFWD, compared with placebo, at doses of 20 and 40 μg TID, but not at 60 μg. From these data, the 40-μg TID dose was tested in a subsequent phase II trial—BERCI-2 (16). This study also demonstrated that both MWD and PFWD were increased significantly in patients receiving beraprost sodium.

The results of the two U.S. beraprost studies are in contrast to the European BERCI-1 and BERCI-2 study outcomes, which demonstrated significant improvements in both PFWD and MWD, as well as QOL, over six months of drug administration (16). A significant difference between the two U.S. trials was the administration of beraprost TID, which was designed to minimize the peak blood levels and minimize study dropout from anticipated prostanoid adverse effects. The current trial was purposefully designed to follow an identical study design as that of BERCI-2 to facilitate a comparison of the results in these two populations. Both trials enrolled a similar number of patients and utilized a comparable formulation of beraprost; nevertheless, the distinct study outcome is striking. Although the current trial did not reproduce the BERCI-2 claudication improvement, the BERCI-2 cohort that received beraprost also suggested a trend toward decreased critical cardiovascular events in the beraprost-treated patients as compared with those assigned to placebo (4.8% in the beraprost group and 8.9% in the placebo group, p = NS). However, the total number of cardiovascular events was relatively low in each of these trials, and therefore, differences can only be regarded as hypothesis-generating.

Analysis of variables that might underlie such differing study outcomes is important to assure that conclusions regarding potential therapeutic efficacy or futility are potentially elucidated. These two large, prospective investigations differ in their study locations, and such geographic distinctions may be associated with enrollment of heterogeneous study cohorts, with potentially differing disease etiologies, PAD severity, use of concomitant treatments, or application of study outcome measurement techniques.

A comparison of the baseline demographic characteristics between the two trials is shown in Table 1. There was no significant difference in age, gender, duration of PAD, baseline claudication distance, or previous limb bypass surgery rates between the two studies. However, the current U.S. trial did include a higher number of patients with hypertension, diabetes, and lipid disorders, as compared with the BERCI-2 trial, and may explain the failure to show efficacy in the present study. It is unknown whether this might affect prostaglandin absorption, distribution, or efficacy of this particular prostaglandin formulation. Also, the baseline ABI and walking distance were somewhat lower in the current study, as compared with the BERCI-2 trial, which may have affected the outcome. Thus, it is possible that differences in the results between the two trials may have been slight differences in baseline demographics between the populations.

Although a lack of efficacy in any oral drug trial can also be surmised to be due to impaired delivery of drug, we consider this to be unlikely, as the adverse effect profile of our subjects strongly indicated that patients randomized to beraprost treatment reported symptoms strongly suggestive of prostaglandin vasodilator effects. We also note that the short half-life of orally administered prostaglandins has long been hypothesized to limit their clinical efficacy in other vascular disease states. This limitation may well be magnified during treatment of claudication, in which the increased metabolic demand of limb muscles during ambulation usually requires a profound and sustained improvement in limb blood flow or muscle metabolic function to be associated with an improvement in claudication symptoms.

Conclusions. The current trial results are in concordance with previous U.S. data and demonstrate that prolonged treatment with oral beraprost does not diminish the symptoms of claudication or improve the QOL of patients with PAD. Whether the use of a more sustained prostaglandin moiety might provide convincing data and proof of efficacy, or whether there are more specific cohorts of patients with PAD that might benefit from prostaglandin use, will require a more precise understanding of the pathophysiology of claudication itself. The potential benefit of beraprost on critical cardiovascular events would require evaluation in a larger, prospective investigation.

Acknowledgments

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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;71:510–5.
2. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286:1317–24.
3. Hiatt WR, Regensteiner JG, Hargarten ME, Wolfel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. Circulation 1990;81:602–9.
4. Klugherz B, Mohler ER III. Current and emerging therapies for lower extremity peripheral arterial disease. ACC Curr J Rev 2001;9:37–9.
5. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med 2001;344:1608–21.
6. Hirsch AT, Reich M. Intermittent claudication. Curr Treat Options Cardiovasc Med 2001;3:167–80.
7. Reilly MP, Mohler ER III. Cilostazol: treatment of intermittent claudication. Ann Pharmacother 2001;35:48–56.
8. Dawson DL, Cutler BS, Meissner MH, Strandness DEJ. Cilostazol has beneficial effects in treatment of intermittent claudication: results from a multicenter, randomized, prospective, double-blind trial. Circulation 1998;98:678–86.
9. Beebe HG, Dawson DL, Cutler BS, et al. A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial. Arch Intern Med 1999;159:2041–50.

10. Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med 2000;109:523–30.
11. Vane JR, Botting RM. Pharmacodynamic profile of prostacyclin. Am J Cardiol 1995;75:3–10A.
12. Friedman R, Mears JG, Barst RJ. Continuous infusion of prostacyclin normalizes plasma markers of endothelial cell injury and platelet aggregation in primary pulmonary hypertension. Circulation 1997;96:2782–4.
13. Willis AL, Smith DL, Vigo C, Kluge AF. Effects of prostacyclin and orally active stable mimetic agent RS-93427-007 on basic mechanisms of atherogenesis. Lancet 1986;2:682–3.
14. Demolis JL, Robert A, Mouren M, Funck-Brentano C, Jaillon P. Pharmacokinetics and platelet antiaggregating effects of beraprost, an oral stable prostacyclin analogue, in healthy volunteers. J Cardiovasc Pharmacol 1993;22:711–6.
15. Nony P, Ffrench P, Girard P, et al. Platelet-aggregation inhibition and hemodynamic effects of beraprost sodium, a new oral prostacyclin derivative: a study in healthy male subjects. Can J Physiol Pharmacol 1996;74:887–93.
16. Lievre M, Morand S, Besse B, Fiessinger JN, Boissel JP, the Beraprost et Claudication Intermittente (BERCI) Research Group. Oral beraprost sodium, a prostaglandin I_2 analogue, for intermittent claudication: a double-blind, randomized, multicenter controlled trial. Circulation 2000;102:426–31.
17. Labs KH, Nehler MR, Roessner M, Jaeger KA, Hiatt WR. Reliability of treadmill testing in peripheral arterial disease: a comparison of a constant load with a graded load treadmill protocol. Vasc Med 1999;4:239–46.
18. Regensteiner JG, Gardner A, Hiatt WR. Exercise testing and exercise rehabilitation for patients with peripheral arterial disease: status in 1997. Vasc Med 1997;2:147–55.
19. Lievre M, Azoulay S, Lion L, Morand S, Girre JP, Boissel JP. A dose-effect study of beraprost sodium in intermittent claudication. J Cardiovasc Pharmacol 1996;27:788–93.

APPENDIX

Critical Cardiovascular Events Committee: Marie Gerhard-Herman, MD, Brigham and Women's Hospital, Boston, Massachusetts; and Wendy Johnson, MD, South Shore Hospital, Weymouth, Massachusetts.

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