Effect of Propionyl-L-carnitine on a Background of Monitored Exercise in Patients With Claudication Secondary to Peripheral Artery Disease

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- **PURPOSE:** Exercise training is established for the treatment of peripheral artery disease; however the additional benefit of pharmacologic therapy with exercise has not been studied. This trial tested the hypothesis that propionyl-L-carnitine (PLC), in combination with monitored home-based exercise training, would improve treadmill peak walking time (PWT) over exercise training alone.
- **METHODS:** Subjects with claudication were randomized to 6 months of therapy with PLC (2 g daily, n = 32) or matching placebo (n = 30). After supervised exercise instruction, all subjects performed exercise training sessions 3 times a week for 30 to 50 minutes/session and compliance was monitored by activity monitors and diary. Change in PWT was the primary outcome measure with other functional assessments predefined as secondary endpoints.
- **RESULTS:** After 6 months of treatment, patients randomized to training and placebo had an increase in PWT of 218 ± 367 seconds, while those randomized to training plus PLC had an increase of 266 ± 243 seconds, $P = .258$. Across the total study cohort, the dose of exercise training (total number of minutes of exercise of at least moderate intensity) was correlated with the change in PWT ($r = 0.259$, $P = .048$), suggesting that the monitored exercise was effective in improving walking performance in both treatment arms.
- **CONCLUSIONS:** In all subjects, the increase in PWT from baseline to month 6 was correlated with the amount of exercise training. However, although favoring PLC, the combination of exercise training and PLC did not result in a statistically significant benefit in peak treadmill performance or quality of life compared with exercise alone.

K E Y W O R D S

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Peripheral artery disease (PAD) is a prevalent manifestation of atherosclerosis associated with the functionally limiting symptom of intermittent claudication. Established and guideline-recommended claudication therapies include a formal, supervised exercise rehabilitation program, pharmacotherapy, and in selected patients, revascularization.[1,2] Supervised exercise rehabilitation is the recommended form of exercise training because home-based programs offer less benefit.[3-8] The potential incremental benefit of pharmacotherapies

for claudication when combined with exercise training has not been demonstrated.

L-Carnitine and propionyl-L-carnitine (PLC) may improve treadmill exercise performance in patients with claudication.[9] In 2 multicenter trials, PLC had clinical benefit defined as improved treadmill walking time and quality of life.[10,11] Small single-center studies suggested that the benefit of exercise training may be augmented by the administration of PLC.[12,13] The current study tested the hypothesis that in patients with claudication, 6 months treatment with PLC in combination with a home-based exercise would improve treadmill peak walking time (PWT) more than exercise alone.

METHODS

This study was a randomized, placebo-controlled, double-blinded, multicenter trial conducted at 10 sites in the United States, from May 2006 through March 2008. The protocol was reviewed by the appropriate institutional review committees and all patients signed informed consent. At screening, patients were assessed with a history, physical examination, and laboratory and hemodynamic tests.[14,15] At this same visit, subjects were further evaluated for inclusion on a fixed-grade treadmill (2 m/h, 12% grade) and subsequently enrolled if they had a PWT between 90 and 360 seconds. Eligible patients were between the ages of 40 and 80 years and had a diagnosis of claudication for at least 1 year with stable disease for at least 3 months. Peripheral artery disease was confirmed by an ankle/brachial index (ABI) 0.90 or less in at least 1 ankle. For subjects with incompressible ankle arteries (ABI $>$ 1.30), a great toe index 0.70 or less in at least 1 leg could be used to establish the diagnosis of PAD. Allowable concomitant medications (including antidiabetic, antihypertensive, hypolipidemic, antiplatelet, and β-blocking drugs) had to be prescribed at stable doses for 3 months before screening.

Exclusion criteria included the following: (*a*) critical leg ischemia; (*b*) peak exercise performance limited by any disease process other than PAD; (*c*) current participation in an exercise program, aortic or lower extremity revascularization within 6 months, major surgery during the last 3 months, or myocardial infarction in the previous 6 months; (*d*) uncontrolled hypertension, renal insufficiency, or abnormal liver function; and (*e*) participation in a claudication clinical trial in the last 6 months or any trial of PLC. Patients receiving pentoxifylline or cilostazol were eligible for participation after a 1-month washout of those drugs.

Subjects who met all inclusion-exclusion criteria entered the run-in phase that consisted of 2 visits approximately a week apart to assess PWT on a graded treadmill protocol. This protocol started at 2 m/h, 0% grade for 2 minutes, with a subsequent 2% increase in grade every 2 minutes up to a maximal grade of 18%, which was maintained until PWT occurred. Mean claudication-limited PWT during run-in had to be within the range 90 to 720 seconds and the variability of PWT had to be 20% or less between the tests (calculated as the difference between the 2 tests divided by the highest PWT value). If the PWT variability was greater than 20%, a third treadmill test was allowed 1 week later, and the last 2 tests then had to be reproducible or the patient was a screen failure. Patients next entered a 2-week period of supervised and home exercise training, which was monitored by an activity monitor (see later). At the end of this run in phase, subjects must have demonstrated compliance with wearing the activity monitor (at least 10 hours a day for at least 5 days between the screening and run in 1 visit). In addition, subjects must have completed 2 supervised and a minimum of 50% of the prescribed home exercise sessions to be eligible for randomization. If the subject was not compliant with the activity monitor, a second compliance period was allowed between run in 1 and 2 visits after which the patient could be randomized when compliance was established. Noncompliant patients were discontinued from the study.

After demonstrating compliance with the exercise and activity monitoring, patients were randomized to receive PLC 2 g/day or matching placebo for 6 months. Follow-up graded treadmill testing was performed at 3 months and 6 months (with 2 tests a week apart at the 6-month visit). On the day of a treadmill, test subjects were instructed not to take their morning dose of study medication.

Exercise Training and Activity Monitoring

Supervised exercise sessions were performed weekly at the study site during 2 weeks of the baseline period as previously described.[4] Each session consisted of 5 minutes of warm-up activities, approximately 50 minutes of intermittent treadmill exercise, and concluded with 5 minutes of cool-down. Exercise training was initiated at 1 to 2 m/h, 0% grade or greater based on individual tolerance, with a goal to induce moderate claudication pain after 3 to 5 minutes of treadmill walking; using a scale of 0 for no pain and 5 for severe pain, this would represent a level of 2 to 3 for mild to moderate pain. These sessions were designed to educate the patients about how exercise could be conducted at home, to address any technical questions and provide motivation. These supervised sessions were repeated monthly during the 6-month treatment period to reinforce key techniques.

Subjects were also asked to wear an activity monitor (StepWatch Activity Monitor produced by OrthoCare Innovations LLC, Oklahoma City, OK) during the supervised training sessions to become familiar with the monitor use.

Subjects were instructed on home-based exercise, including recommendations for exercise 2 times per week during run-in and 3 times per week after randomization for the duration of study participation. Counseling on the home training exercise prescription was provided by the site staff and was based on the same method utilized in the supervised sessions except that subjects could employ other walking exercise activities when a treadmill was not available at home. Acceptable home training activities included walking on a treadmill or walking on a track in a mall or gymnasium with an unobstructed path. Subjects were asked to record each exercise session on a patient exercise diary, and each individual exercise training record was reviewed by the site staff and feedback provided on a monthly basis. In addition, subjects were instructed to wear the activity monitor for 10 minutes prior to exercise, during warm-up, exercise, cool-down, and 10 minutes after exercise. In addition to use during exercise training sessions, subjects were instructed to wear the activity monitor every day for at least 10 hours per day for a week during screening, after month 3 and after month 6 to provide a measure of ambulatory activity in a natural setting.

Definitions of Terms

For the primary analysis, a *completed exercise training session* was defined as concordant evidence of training on both the diary and activity monitor. The scheduled supervised exercise sessions performed at the study sites were counted as completed sessions. Activity monitor confirmation of exercise required at least 10 minutes (within a 50-minute window) of moderate activity on the activity monitor (10 steps per minute or more) within 1 hour prior to the diary start time or 1 hour after diary denoted stop time. The 50-minute window corresponded to the protocol recommended total exercise session duration. If more than one 50-minute exercise interval was observed from the monitor, the interval closest to the diary endpoint was selected. This algorithm created a binary indicator of training for each subject for each day between randomization and the date of last treatment or last follow-up date. *Exercise compliance* was calculated as the total number of completed exercise sessions divided by 72 (total prescribed exercise sessions over 24 weeks). The *dose of exercise* was defined as the total duration (in minutes) of exercise of at least moderate intensity as recorded by the activity monitor during exercise training sessions over the course of the study, which reflects the total amount of exercise training by the subject. *Drug compliance* was calculated as the total number of pills dispensed during treatment period minus the number of pills returned during and after the treatment period count divided by 700 (the total prescribed pills for 25 weeks).

Outcome Assessments

Peak walking time was the primary endpoint and was defined as the maximum amount of time the subject could walk on the treadmill before having to stop because of intolerable claudication symptoms. *Claudication onset time* was a secondary endpoint and was defined as the time when the subject first experienced claudication symptoms. Patient-based questionnaire assessment of functional activity served as secondary endpoints and was assessed with the Walking Impairment Questionnaire (WIQ) and the Medical Outcomes Study 36-Item Short Form (SF-36).[16,17] Ambulatory activity during subject normal activities was characterized as the number of minutes the activity monitor was worn for which the activity level was 10 steps per minute or more divided by total minutes of wear. Thus, when expressed as "minutes," this is the fraction of total wear time where activity exceeded 10 steps per minute. When expressed as "steps," it is the total number of steps taken during periods of moderate (>10 steps per minute) activity divided by the total minutes of wear and is thus steps per minute of wear. At baseline and after 6 months, blood was drawn for plasma carnitine and acylcarnitine concentrations.

Sample Size

Sample size calculations were based on subsets of data from prior placebo-controlled trials of PLC in the treatment of claudication.[11,18] This included data from 66 subjects who received any form of concomitant exercise (unsupervised and supervised), which resulted in an anticipated difference between groups of 114.3 m. Based on a 2-sample unequal variance *t* test, with a significance level of .05 and 95% power, 26 subjects would be required in each treatment group to confirm such a difference in PWT. The sample size for the proposed study was increased to 32 subjects per group to allow for a 20% dropout rate at 6 months.

Statistical Analysis

The primary endpoint was the change in PWT from the average of the last 2 treadmill tests at baseline to the average of the 2 treadmill tests performed at month 6. The predefined primary analysis was performed in the modified intent-to-treat (mITT) population of all randomized subjects who received study medication and had at least 1 postbaseline evaluation

of PWT. In the primary analysis, a last observation carried forward method was used for subjects who dropped out of the study prematurely. A per-protocol population was also defined, which included all subjects in the mITT population who were greater than 75% compliant with drug and greater than 75% compliant with exercise training (as defined by the diary only) and had no major protocol violations.

All statistical tests were 2-sided and tested at the .05 level of significance. The primary analysis began with an analysis of covariance, but since the data were not normally distributed, a natural log transformation of the ratio of month 6/baseline PWT was applied to reduce the effect of extreme values as prespecified before unblinding. Independent variables in the final model were baseline PWT, treatment group, site, and exercise session compliance. The treatment-by-site and treatment-by-exercise session compliance interactions were also included and tested for at the .10 significance level. The analyses of questionnaire data used a Cochran Mantel Haenszel test of the residuals from the analysis of covariance model adjusted for treatment.

RESULTS

There were 128 subjects evaluated, of which 59 were not randomized (Figure 1). In the 59 patients not randomized, 51 failed to meet the study inclusion/exclusion criteria at the screening visit and 8 patients were excluded during run-in (did not meet graded treadmill reproducibility, PWT out of range, or noncompliance with activity monitor). None were dropped because of lack of compliance with exercise training during the run-in period.

In patients who met all entry criteria, 69 were randomized and received study drug but 62 subjects were included in the mITT population based on having 1 postrandomization treadmill test (Figure 1). Baseline characteristics of the mITT population were typical of patients with PAD (Table 1). The mean age was approximately 67 years; most were white males who were current or former smokers. Over two-thirds of patients were taking an antiplatelet agent (aspirin or clopidogrel) but only approximately half were on a statin drug. The only imbalance was a lower proportion of patients with diabetes randomized to PLC.

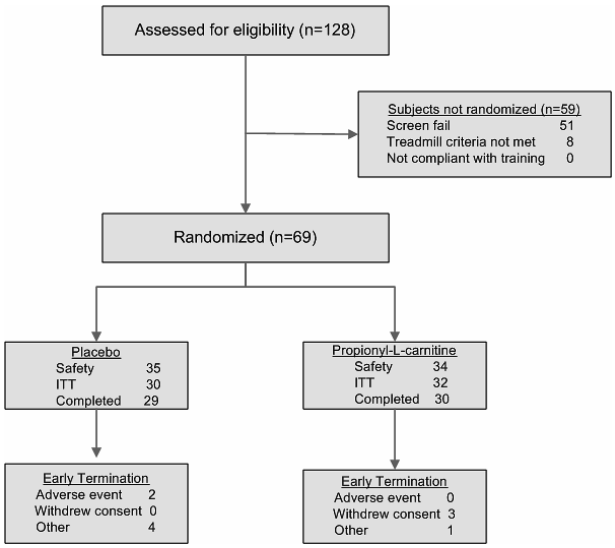

Figure 1. Patient disposition. The most common reasons for exclusion at the screening visit (some patients met more than 1 exclusion criterion) included fixed treadmill peak walking time outside of prespecified range (n = 18), resting ankle brachial index not meeting criteria (n = 17), and treadmill exercise not limited by claudication (n = 13). Additional reasons of note included inability to participate in an exercise training program (n = 4) and peripheral artery disease of a nonatherosclerotic nature (n = 2). Abbreviation: ITT, intention-to-treat.

Compliance With Medication and Exercise Training

Compliance with study drug treatment was high (mean of 100.5% on PLC and 98.1% on placebo), but compliance with the exercise program was less (60.2% placebo and 73.7% PLC). One patient on PLC and 4 on placebo were more than 120% compliant with the exercise program (averaged more than 3.6

Table 1 • Baseline Characteristics in the Modified Intent-to-Treat Population[a]

	Placebo	PLC
n	30	32
Age, y	66.6 ± 8.8	67.4 ± 8.7
Gender, male:female	25:5	20:12
Race, %		
White	76.7	84.4
Black	20.0	15.6
Other	3.3	0.0
Body mass index, kg/m^2	28.5 ± 4.4	28.5 ± 4.5
Diabetes, %	33.3	9.4[b]
Smoking status, %		
Never	10.0	0.0
Previous	73.3	62.5
Current	16.7	37.5
C-reactive protein, mg/L	4.9 ± 4.4	5.3 ± 3.9
Ankle brachial index	.70 ± 0.18	.70 ± 0.15
Concomitant medications, %		
Aspirin	66.7	81.3
Clopidogrel	13.3	12.5
Statin	53.3	46.9

Abbreviation: PLC, propionyl-L-carnitine.
[a]Continuous variables are reported as mean ± standard deviation.
[b]There were fewer patients with diabetes randomized to PLC than placebo, $P = .029$.

exercise sessions per week), whereas 16 on PLC and 20 on placebo were less than 75% compliant.

Effect of Treatment on PWT, Ambulatory Activity, and Quality of Life

Patients randomized to PLC and exercise had a 75.2% increase in PWT, whereas those on placebo had a 64.4% increase (Table 2 and Figure 2). The primary analysis based on log-transformed data resulted in a geometric mean difference of 17.2 seconds in favor of PLC (95% confidence interval, −12.3 to 46.6, P = .258). Similarly, no statistically significant effect of PLC was seen on claudication onset time at 6 months (geometric mean difference 34.2 seconds in favor of PLC, 95% confidence interval, −12.3 to 80.6, P = .154).

At baseline, 84% of PLC subjects and 83% of placebo patients recorded at least 10 hours of ambulatory activity, which was at a moderate level 18 ± 9.5% of the wear time in placebo patients and 16 ± 6% of the wear time in the PLC group. Monitoring compliance decreased over time and by month 6, only 66% of PLC and 60% of placebo subjects recorded ambulatory activity. Using the evaluable data (patient with baseline and month 6 data), there were no changes in minutes of ambulatory activity in either group over 3 and 6 months. After 6 months, ambulatory activity had increased 1 ± 8% on placebo and 0 ± 5% on drug.

At baseline, all patients had impairments in SF-36 physical component and physical function scores (Table 3). Over the 6 months of study, scores in these domains improved in both treatment groups, but with no statistically significant differences between groups. Similarly, comparable improvements in WIQ speed and distance scores were observed in each group (Table 4).

Table 2 • Baseline Exercise Performance and Change at 12 and 24 Weeks[a]

	Placebo	PLC
PWT, s[b]		
Baseline	339 ± 150	354 ± 143
Δ12 wk	+152 ± 210	+169 ± 157
Δ24 wk	+218 ± 367	+266 ± 243
COT, s[c]		
Baseline	60 ± 24	69 ± 35
Δ12 wk	+68 ± 88	+97 ± 107
Δ24 wk	+100 ± 100	+174 ± 183

Abbreviations: COT, claudication onset time; PLC, propionyl-L-carnitine; PWT, peak walking time.
[a]Continuous variables are reported as mean ± standard deviation.
Δ indicates change from baseline (seconds).
[b]The geometric mean difference between propionyl-L-carnitine and placebo on PWT was 17.2 s (95% confidence interval −12.3 to 46.6), P = .258.
[c]The geometric mean difference between propionyl-L-carnitine and placebo on COT was 34.2 s (95% confidence interval −12.3 to 80.6), P = .154.
Abbreviations: COT, claudication onset time; PLC, propionyl-L-carnitine; PWT, peak walking time.

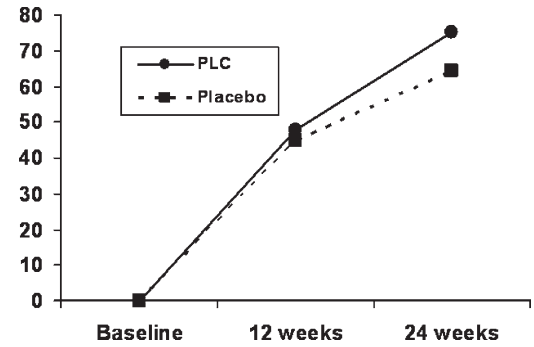

Figure 2. Percent change in peak walking time from baseline to 12 and 24 weeks, modified intention-to-treat population. The percent change in peak walking time from baseline to 12 and 24 weeks is demonstrated for subjects randomized to drug or placebo. Abbreviation: PLC, propionyl-L-carnitine.

Correlates With Peak Walking Time

Despite the absence of group improvements, across the entire study cohort the individual subject changes in minutes of ambulatory activity from baseline to month 6 correlated with the change in PWT (r = 0.34, P = .013). Similarly, the dose of training exercise correlated with the change in PWT (r = 0.259, P = .048).

Plasma Carnitine Pool

Six-month treatment with PLC was associated with increases in carnitine, acetylcarnitine, propionylcarnitine, and total carnitine concentrations with no changes on placebo (Table 4). Previous reports of exercise training in PAD have demonstrated an inverse correlation between changes in the plasma carnitine pool and the increase in PWT.[19] In the mITT population, the ratio of acylcarnitine to free-carnitine demonstrated a nonsignificant inverse correlation (r = −0.20); however, in the per-protocol population, this relationship was significant (r = −0.33, P = .045).

Safety

Adverse events were described in 70.6% of patients on drug and 68.6% on placebo. Adverse events that affected more than 5% of subjects in either group with a ratio more than 1.5 PLC versus placebo included nausea, diarrhea, bronchitis, and back pain. Serious adverse events on PLC included 2 pneumonias and 1 each of chronic obstructive pulmonary disease and pulmonary embolism. In placebo-treated patients, serious adverse events included 1 each of pneumonia, atrial fibrillation, coronary artery disease, myocardial infarction, gastric ulcer, and transient ischemic attack.

Table 3 • Questionnaire Assessments at Baseline and Change After 6 Months[a]

	Placebo		PLC	
	Baseline	Δ mo 6	Baseline	Δ mo 6
SF-36 physical component	32.6 ± 7.40	+3.3 ± 7.56	35.8 ± 8.63	+4.2 ± 7.17
SF-36 physical function	41.2 ± 15.7	+8.8 ± 23.2	49.5 ± 16.7	+12.7 ± 11.5
WIQ distance	17.7 ± 18.6	+20.9 ± 28.2	21.6 ± 20.0	+27.9 ± 20.9
WIQ speed	22.8 ± 15.8	+6.6 ± 17.8	30.6 ± 22.2	+12.2 ± 19.6

Abbreviations: PLC, propionyl-L-carnitine; SF-36, Medical Outcomes Study 36-Item Short Form; WIQ, Walking Impairment Questionnaire.
[a]Positive changes indicate improvement.

DISCUSSION

This study did not demonstrate a statistically significant benefit of PLC when added to a background of exercise training in patients with symptomatic PAD. Interestingly, the numerical difference in PWT between groups favoring PLC was similar to that observed in previous studies, suggesting that the current study was underpowered to detect this difference.[11,18] Similarly, although the functional status questionnaires showed no statistical difference between treatment arms, there was a numeric trend favoring PLC for all parameters, which is consistent with the trend in the primary endpoint.

Both study groups showed large increases in PWT, which were considerably greater than the expected placebo response based on previous drug clinical trials (ranging from 18% to 25%).[11,20] This large increase on placebo suggests an effective training response to the background exercise program. This is further supported by the relationship between dose of exercise and change in PWT in the combined drug and placebo groups (more training, greater benefit), as well as the overall changes in the SF-36 and WIQ scores. This apparent benefit is in contrast to previous efforts to use home training strategies in the PAD population.[6,7] This suggests that the use of periodic reinforcement and retraining based on home monitoring tools (monitored training) may be important strategies to increasing access to the benefits of exercise training in PAD patients. The change in PWT in the total study population correlated with change in ambulatory activity. This provides further support for the use of treadmill PWT as a surrogate for patient function in their normal activities, consistent with numerous previous reports.[16,21,22]

Table 4 • Carnitine and Acylcarnitine Plasma Measurements at Baseline and After 6 Months

	Placebo	PLC
Carnitine, nmol/mL		
Baseline	41.6 ± 6.4	42.1 ± 7.5
Δ 24 wk	−3.2 ± 10.7	4.8 ± 8.6[c]
Acetylcarnitine, nmol/mL		
Baseline	8.8 ± 3.3	8.6 ± 4.5
Δ 24 wk	−0.1 ± 2.5	2.2 ± 3.9[b]
Propionylcarnitine, nmol/mL		
Baseline	0.48 ± 0.19	0.51 ± 0.33
Δ 24 wk	0.01 ± 0.22	0.13 ± 0.45
Total carnitine, nmol/mL[a]		
Baseline	47.1 ± 8.9	47.2 ± 8.4
Δ 24 wk	−2.7 ± 8.8	6.0 ± 8.6[c]

Abbreviation: PLC, propionyl-L-carnitine.
[a]Total carnitine is carnitine plus all acylcarnitines.
[b]$P < .05$.
[c]$P < .01$.

The clinical benefits of PLC have been suggested in several small trials with intravenous or oral administration.[9,10,23,24] Two large multicenter trials demonstrated positive results with PLC on the primary endpoint of peak exercise performance on the treadmill, supported by parallel increases in quality-of-life assessments.[11,18] The mechanism of PLC benefit in PAD is incompletely understood. However, PLC enters muscle and is converted to propionyl-CoA and carnitine.[25] These are both important metabolic intermediates with the potential to modify dysfunctional muscle metabolic function, a hypothesized contributor to exercise limitation in PAD.[26] Similarly, exercise training may have positive metabolic effects[27] and other work has suggested benefits to adding carnitine or acylcarnitine supplementation to exercise training.[13] Although the plasma carnitine pool is poorly reflective of the muscle carnitine pool,[28] the changes observed with PLC treatment (Table 4) support PLC access to a metabolically active cellular carnitine pool. Nonetheless, no significant functional improvement was observed in the studied patients in response to PLC treatment.

Limitations

Although a nonsignificant benefit was observed for PLC combined with exercise, the lack of statistical

significance was in part due to the limited sample size. In addition, the prescription of background exercise could have influenced the results based on individual responses. For example, 1 patient randomized to placebo had a large increase in PWT from entry to exit. The site investigator discovered that this patient was very compliant with the exercise program but not compliant with recording this exercise in the diary or use of the activity monitor. A sensitivity analysis was performed by removing this patient from the placebo group, which revealed an improvement in the *P* value for the primary analysis of PLC effect on PWT from .258 to .096. Thus, in studies that employ drug therapy on a background of exercise training, accurate recording of the dose and compliance with the exercise intervention is critical in being able to detect any drug effect over the background exercise training response. In addition, an apparent imbalance between groups occurred in the distribution of women and in persons with diabetes, which also may reflect the small sample size.

In summary, patients treated with background exercise training, whether randomized to drug or placebo, had an overall increase in PWT. However, the combination of exercise training and propionyl-L-carnitine with the experimental conditions tested in this trial, although favoring PLC, did not confirm the original hypothesis and did not result in a statistically significant benefit in peak treadmill performance or quality of life when compared with exercise training alone. Monitored home exercise may be a useful modality for prescribing exercise in patients with claudication.

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