Peripheral Vascular Disease

European Multicenter Study on Propionyl-L-Carnitine in Intermittent Claudication

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OBJECTIVES	This study was performed to identify a target population of claudicants for propionyl-L-carnitine treatment.
BACKGROUND	Previous studies suggest that the efficacy of propionyl-L-carnitine in intermittent claudication is greater in patients with severe functional impairment than in those with mild walking disability.
METHODS	After run-in, 485 claudicant patients were randomized to placebo or propionyl-L-carnitine (1 g bid, po) and then stratified on the basis of maximal walking distance (cutoff point 250 m) and maximal walking distance variability (cutoff point 25%). Treatment lasted 12 months. Walking capacity was assessed by treadmill and quality of life by a questionnaire exploring various aspects of daily life.
RESULTS	In the target population, that is, patients who at baseline walked ≤250 m and showed a maximal walking distance variability ≤25%, per-protocol analysis showed that the effect of propinyl-L-carnitine was significantly greater than that with placebo for both maximal walking distance and initial claudication distance (ICD). In the intention-to-treat population, maximal walking distance increased by 62 ± 14% on propionyl-L-carnitine and by 46 ± 9% (p < 0.05) on placebo, while no difference between treatments was observed for ICD. The beneficial effect of propionyl-L-carnitine was confirmed when data of the target population were pooled with those of patients who at baseline walked ≤250 m and showed a >25% maximal walking distance <50% variability. Actually, maximal walking distance increased by 98 ± 16% in the propionyl-L-carnitine group and by only 54 ± 10% in the placebo group (p < 0.01). The corresponding values for ICD were 99 ± 21% and 51 ± 8% (p < 0.05). For patients with baseline maximal walking distance >250 m, no difference between treatments was observed.
CONCLUSIONS	Claudicants with maximal walking distance ≤250 m benefited from the use of propionyl-L-carnitine, with improvement in walking distance and quality of life. However, patients with mild functional impairment (i.e., walking distance >250 m) showed no response to propionyl-L-carnitine. (J Am Coll Cardiol 1999;34:1618–24) © 1999 by the American College of Cardiology

Patients with peripheral arterial disease have alterations in carnitine metabolism that seem to be related to the severity of circulatory insufficiency (1–4). In such patients, carnitine supplementation restores a normal carnitine homeostasis, improves the efficiency of oxidative phosphorylation and lessens symptoms of claudication (4,5). Propionyl-L-carnitine, one of the most potent analogues of carnitine (6), exerts a greater effect on walking capacity than that with an equimolar dose of carnitine (7). When given orally, it has been reported to be a well-tolerated drug, effective in improving walking capacity and quality of life in patients with intermittent claudication (8,9).

Propionyl-L-carnitine efficacy seems to be greater in patients with the lowest walking capacity than in those with mild functional impairment (9). This observation, however, is based on a post hoc analysis and, consequently, may be affected by unequal distribution of the prognostic variable. The present multicenter trial in Europe was undertaken to prospectively investigate whether propionyl-L-carnitine treatment outcome is more favorable in patients with severe functional impairment than in those with less pronounced walking disability.

METHODS

Patients. Patients affected by intermittent claudication for at least one year were selected. The diagnosis was established on the basis of history, Doppler examination and

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Abbreviations and Acronyms

ABPI = ankle-brachial pressure index
ICD = initial claudication distance
MWD = maximum walking distance

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decrease in ankle-brachial pressure index (ABPI) after exercise. Only patients with a resting ABPI <0.80 that decreased with exercise by at least 20% and a maximum walking distance (MWD) between 50 and 400 m (as tested by treadmill, speed 3 km/h, inclination 7%) were included in the study. Three treadmill tests were conducted at three-week intervals during the run-in period, and only patients in whom the highest value of MWD during the three tests did not exceed the lowest one by more than 50% were included. The cardiovascular drugs allowed during the study were diuretics, lipid-lowering agents, calcium antagonists, ACE inhibitors, nitrates and aspirin. Major exclusion criteria were reconstructive vascular surgery, angioplasty or sympathectomy during the previous six months, peripheral neuropathy and any other condition that limited exercise capacity.

Study design. A double-blind, placebo-controlled, parallel design was adopted by 38 centers for the study. All patients gave written informed consent before participation. Furthermore, ethical approval for the study was obtained at all participating centers. After the screening visit, all current treatments for intermittent claudication were discontinued, and patients entered a two-week phase during which they were familiarized with the treadmill. A nine-week, single-blind placebo, run-in period followed, during which stability of the MWD was assessed. At the end of this period, patients who met the inclusion criteria were randomly allocated to placebo or propionyl-L-carnitine (1 g bid, po). At randomization, patients were stratified on two variables: MWD (cutoff point 250 m) and MWD variability (cutoff point 25%). Thus, patients were divided into four strata (Table 1). S_1 population (i.e., patients who at baseline walked ≤250 m and showed a MWD variability ≤25%) was prospectively identified as the target population. The double-blind medication lasted one year. Distance walked before onset of claudication (initial claudication distance [ICD]) and MWD measured by treadmill, as previously described, were assessed monthly for the first two months and then at two-month intervals. A quality-of-life questionnaire (Table 2) was completed by the patients at the end of

Table 2. Quality-of-Life Questionnaire

1. Walking/pain
   a. Leg pain while walking
   b. Going upstairs
   c. Going downstairs
   d. Walking speed
   e. Recovery time after claudication pain
   f. Leg pain at rest
2. Global physical function
   a. Outdoor activies, e.g., shopping
   b. Indoor activies, e.g., housework
   c. Difficulty while standing
   d. Tiredness
   e. Feeling of physical limitation
3. Social function
   a. Family
   b. Friends
   c. Leisure activities
   d. Holiday
   e. Work
   f. Sexual life
4. Psychological attitudes
   a. Sleep
   b. Depression
   c. Anxiety
   d. Irritability
   e. Feeling limitation

the run-in phase and three months apart, during the treatment period, before the treadmill test. The items of the questionnaire were rated by patients from 1 to 5 (1 = extremely good function, 5 = extremely poor function). Thus, the higher the score, the worse the function. The methodological approach to the construction of the questionnaire was that suggested by Jaeschke and Guyatt (10). The questionnaire was translated into the languages of the countries participating in the study and then retranslated into Italian to confirm its accuracy.

Electrocardiographic and routine biochemical and hematologic tests were performed at the end of the run-in period and every two months during the double-blind phase. Drug compliance was assessed by tablet count without the patient's knowledge. Patients taking <75% of the prescribed dose were noncompliant and considered as dropouts. Although all participants were advised of the beneficial effects of a therapeutic walking program and nicotine abstinence, no persistent effort was made to change their lifestyle.

Statistical analysis. Primary efficacy end point was the change in MWD from baseline to the end of the treatment period. The secondary end points were the change in ICD and in quality-of-life questionnaire scores. For the computation of percent difference from baseline, we utilized the following formula:

(month 12 value − baseline value × 100)/baseline value

Table 1. Patients Stratification

	Stratum 1 (S_1)	Stratum 2 (S_2)	Stratum 3 (S_3)	Stratum 4 (S_4)
MWD (m)	≤ 250	≤ 250	> 250	> 250
MWD variability	≤ 25%	> 25 ≤ 50%	≤ 25%	> 25 ≤ 50%

MWD = maximum walking distance.

Table 3. Characteristics of 485 Intention-to-Treat Patients

	PLC Group (n = 239)	Placebo Group (n = 246)
Age (yr)	61.9 ± 0.57	62.7 ± 0.57
Male	204 (84)	195 (79)
Female	38 (16)	51 (21)
Smoker	208 (87)	209 (85)
Diabetic	12 (5)	12 (5)
Systolic blood pressure (mm Hg)	143.7 ± 1.08	144.2 ± 1.05
Diastolic blood pressure (mm Hg)	81.4 ± 0.47	81.1 ± 0.54
Ankle brachial index at rest	0.6 ± 0.01	0.6 ± 0.01
Initial claudication distance (m)	141.5 ± 4.59	143.0 ± 4.32
Maximum walking distance (m)	234.8 ± 6.12	240.9 ± 5.91

Data are presented as mean ± SE or number (%) of patients.
    PLC = propionyl-L-carnitine.

Due to nonnormality of distributions and heterogeneity of treatment variances, comparison of treatment effects was made by a nonparametric procedure. We used the Generalized Cochran-Mantel-Haenszel test stratified by center according to randomization and conducted on within-center standardized midranks of original changes from baseline (11). Both per-protocol and intention-to-treat population were analyzed.

Data are expressed as mean value ± standard error. Baseline values of ICD and MWD are the mean values of the three measurements taken during the run-in phase.

RESULTS

Out of 1,773 patients screened, 501 patients were randomized. Among these, 16 (9 in the propionyl-L-carnitine group, 7 in the placebo group) discontinued the study before the first visit at month 1. The remaining 485 patients were considered the intention-to-treat population (Table 3). Only 328 patients completed the one-year protocol, 162 in the propionyl-L-carnitine group and 166 in the placebo group. Actually, 77 patients in the propionyl-L-carnitine group and 80 in the placebo group dropped out of the study for various reasons. In particular, five patients on propionyl-L-carnitine and five on placebo died. Adverse events requiring treatment discontinuation were 27 in the propionyl-L-carnitine group and 30 in the placebo group. Protocol violation was observed in 27 patients randomized to propionyl-L-carnitine and 34 randomized to placebo. Finally, 18 patients on propionyl-L-carnitine and 11 on placebo were lost to follow-up.

With the exception of walking performance, no difference in clinical characteristics was observed between the four subsets of patients obtained by stratification. No patients stopped smoking during the study.

Table 4. Effect of Treatments on Walking Capacity in the Per-Protocol Population Who at Baseline Showed MWD ≤ 250 m and MWD Variability ≤ 25% (S_1 Population)

|	Initial Claudication Distance		Maximum Walking Capacity	
	Placebo (n = 61)	PLC (n = 53)	Placebo (n = 61)	PLC (n = 53)
Baseline	110 ± 5	102 ± 6	176 ± 7	159 ± 7
Month 12	163 ± 12	198 ± 22	263 ± 21	300 ± 33
Percent change	48 ± 9	109 ± 31	46 ± 9	87 ± 20
	$p < 0.01$		$p < 0.01$	

PLC = propionyl-L-carnitine.

Effect on walking capacity. Results observed in S_1 population, that is, the target population, are shown in Table 4. The per-protocol approach showed that, after 12 months of treatment, the effect of propionyl-L-carnitine on both MWD and ICD was significantly greater than that with placebo. In the intention-to-treat population MWD increased from 171 ± 6 to 256 ± 20 m in the placebo group (n = 83) and from 162 ± 6 to 266 ± 24 m in the propionyl-L-carnitine group (n = 80). Group differences significantly favored propionyl-L-carnitine (p < 0.05). Conversely, no difference between treatments was observed for ICD.

In S_2 population, after treatment, MWD increased from 169 ± 9 to 283 ± 41 m in the placebo group (n = 26) and from 184 ± 8 to 411 ± 58 m in the propionyl-L-carnitine group (n = 33). Although the superiority of propionyl-L-carnitine versus placebo was markedly greater in this subset of patients than in S_1 population, difference between treatments was not statistically significant. Similarly, no statistical difference between treatments was observed for ICD, which increased from 93 ± 4 to 140 ± 18 m in the placebo group and from 107 ± 5 to 185 ± 31 m in the propionyl-L-carnitine group. However, a significant improvement in walking capacity with propionyl-L-carnitine was observed when data of S_1 and S_2 population were pooled. Actually, in S_1 + S_2 population, per-protocol analysis showed that MWD increased by 98 ± 16% (from 169 ± 5 to 342 ± 30 m) in the propionyl-L-carnitine group (n = 86) and only by 54 ± 10% (from 174 ± 5 to 269 ± 19 m) in the placebo group (n = 87). Difference between treatments was statistically significant (p < 0.01). In the same patients, ICD increased by 99 ± 21% (from 104 ± 4 to 193 ± 17 m) on propionyl-L-carnitine and by 51 ± 8% (from 105 ± 4 to 156 ± 10 m) on placebo (p < 0.05). Figure 1 shows percent changes in MWD and ICD observed throughout the study in S_1 and S_1 + S_2 per-protocol population. By the intention-to-treat approach, superiority of propionyl-L-carnitine versus placebo did not reach statistical significance in S_1 + S_2 population, although in this subset of patients, treatment differences at month 12 favored propionyl-L-carnitine for MWD more so than in S_1 population.

For patients with baseline MWD >250 m, no difference
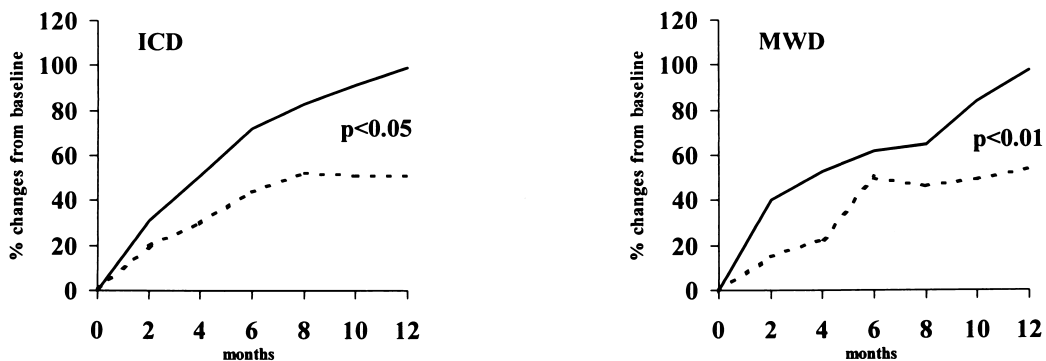
S1 POPULATION
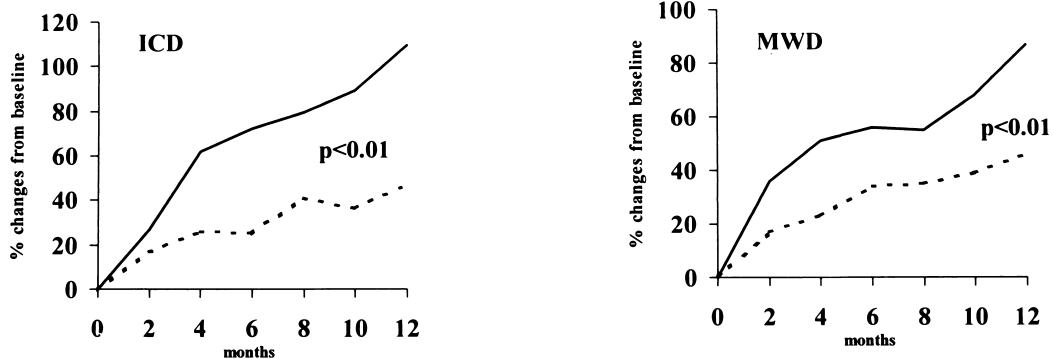
S1+S2 POPULATION

Figure 1. Percent changes in ICD and MWD observed throughout the study in the S_1 and $S_1 + S_2$ per-protocol population. **(Dotted line)** Changes in placebo group; **(solid line)** changes in propionyl-L-carnitine group.

between placebo and active treatment was observed either in those with low (S_3 population) and those with high (S_4 population) MWD variability at baseline. Similarly, no difference between treatments was observed in $S_3 + S_4$ population. Per-protocol analysis showed that MWD increased from 323 ± 4 to 612 ± 37 m in the placebo group (n = 79) and from 332 ± 5 to 574 ± 37 m in the propionyl-L-carnitine (n = 76). Initial claudication distance changed from 196 ± 7 to 381 ± 33 m on placebo and from 202 ± 8 to 367 ± 31 m on propionyl-L-carnitine.

Effect on quality of life. In the per-protocol population, the effect with propionyl-L-carnitine was found to be greater than that with placebo for walking pain, global physical activity and psychological attitudes, whereas social function was not affected by active treatment (Table 5). Similar results were observed with the intention-to-treat approach. In S_2 population, no difference between treatments was observed. Conversely, in $S_1 + S_2$ population, per-protocol analysis showed that the effect of propionyl-L-carnitine was significantly greater than that with placebo for walking/pain (p < 0.05) and global physical activity (p < 0.05). For patients who walked >250 m at baseline,

that is, $S_3 + S_4$ population, no difference between treatments was observed.

Adverse events and fate of the claudicant limb. In the propionyl-L-carnitine group, 5 patients died during the study (4 from cardiovascular causes), and 27 discontinued the treatment because of the occurrence of serious adverse events (cardiac = 5, cerebral = 3, peripheral = 12, others = 7). In the placebo group, deaths were 5 (4 from cardiovascular causes), and the adverse events requiring drug discontinuation were 30 (cardiac = 5, cerebral = 2, peripheral = 13, others = 10). Adverse events not requiring drug

Table 5. Quality-of-Life Questionnaire Scores: Changes from Baseline to Month 12 in S_1 Per-Protocol Population

	PLC (n = 53)	Placebo (n = 61)	p
Walking/pain	-3.8 ± 0.7	-2.1 ± 0.5	<0.01
Global physical function	-2.3 ± 0.7	-0.4 ± 0.5	<0.05
Social function	-1.3 ± 0.4	-0.4 ± 0.4	0.12
Psychological attitudes	-2.1 ± 0.6	-0.3 ± 0.4	<0.01

PLC = propionyl-L-carnitine.

discontinuation were 38 in the propionyl-L-carnitine group and 98 in the placebo group; flu syndrome was the most frequent effect.

With respect to the fate of the claudicant limb, during the 12 months of follow-up, none of the patients underwent amputations, while two patients (0.8%) in the propionyl-L-carnitine group required arterial reconstruction. There were two thromboembolisms of the affected limb (0.8%) in the propionyl-L-carnitine group and three (1.2%) in the placebo group. One patient in the propionyl-L-carnitine group developed a venous ulcer in the nonaffected limb. Five patients (2.1%) in the propionyl-L-carnitine group and 10 (4.1%) in the placebo group progressed to Fontaine's stage III (pain at rest), while progression to stage IV (trophic lesions) was observed in two patients (0.8%) in the propionyl-L-carnitine group and in none of the placebo group. Given the spontaneous fluctuations in intermittent claudication, only changes in MWD ≥50% from the study entry to the final observation were assumed as clinically significant. According to this criterion, in $S_1 + S_2$ population, walking capacity improved in 30 patients (34%) on placebo and in 49 (57%) on propionyl-L-carnitine (p < 0.01). Maximum walking distance deterioration ≥50% was not observed in any patient of both groups. In $S_3 + S_4$ population, MWD improved in 41 patients (54%) on placebo and in 37 (48%) on propionyl-L-carnitine. Also in this subpopulation, no patient experienced an MWD deterioration ≥50%.

DISCUSSION

The present study was designed to verify the hypothesis that propionyl-L-carnitine efficacy in intermittent claudication is higher in patients with severe functional impairment than in those with less pronounced walking disability.

Trial design and statistical analysis. The trial was designed taking into account problems and inadequacies of previous drug trials in intermittent claudication. Different from previous studies not including patients with a walking capacity variability >25% to 30%, the present trial also included patients with a >25% MWD variability <50%, to increase the population representativeness. However, to avoid a major imbalance between groups for a variable related to outcome, patients were stratified on MWD variability at baseline. Stratification on the maximum distance walked was necessary to balance the two treatment groups respecting the number of patients with low and high walking capacity in the groups. Treatment lasted 12 months, much more than the large majority of therapeutic trials in intermittent claudication. This was done to be sure that treatment tolerance to the active drug does not occur. Maximum walking distance was chosen as primary efficacy end point for two reasons. First, changes in carnitine metabolism take place (12), and thus, carnitine supplementation needs (7), only when exercise is of sufficient intensity to qualitatively alter muscle substrate metabolism. Further-

more, many patients with intermittent claudication are still able to continue walking for a long distance after pain onset in the affected leg and thus experience few limitations in daily activities. Thus, MWD, which accurately reflects the impairment experienced by such patients in daily life (13), has greater clinical relevance than ICD.

The statistical analysis was performed both in the intention-to-treat and per-protocol population. Intention-to-treat is a rigorous analysis. In dropouts who provided at least one postbaseline MWD value, the last valid observation was carried forward and used for the analyses at later, missed visits. The disadvantage of the type of analysis, however, is that it tends to mask treatment effects that increase over time.

Walking capacity. This study indicates that claudicants with baseline MWD ≤250 m, after 12 months of treatment with propionyl-L-carnitine, walked a longer distance than those who received placebo. This is a relevant result because the overall clinical utility of pentoxifylline, the most widely used drug for claudication, is limited by drug intolerance and inconsistent clinical response (15–17). Two previous studies reported that propionyl-L-carnitine improved MWD versus placebo by 26% and 27%, respectively (8,14). These improvements were observed in a general population of claudicants and are lower than the 44% improvements observed in our target population. In patients with baseline MWD >250 m, no significant difference was found between treatments. Therefore, findings of the present study are consistent with the previous observation that, in intermittent claudication, only the most affected patients require carnitine supplementation, because they, and not those with mild functional impairment, have reduced availability of endogenous carnitine to meet the increased metabolic demand induced by walking (7).

Quality of life. Propionyl-L-carnitine-induced improvement in walking capacity resulted in a real functional benefit for claudicants. Actually, in $S_1 + S_2$ population, a significant improvement was observed for walking/pain, global physical activity and psychological attitudes.

Concern is often expressed that quality of life methods may not be equally valid for all countries. Westernized countries, however, probably share a cultural uniformity of life-style, values and health beliefs. Actually, quality of life measures have been incorporated in several multinational trials (18–20). Our questionnaire showed a high reliability, as assessed by internal consistency and responses to retesting (G. Brevetti, personal communication). Furthermore, it is valid as evidenced by the finding that it discriminated appropriately among patients with differing degrees of functional impairment. Actually, baseline questionnaire scores in $S_1 + S_2$ population were higher than in $S_3 + S_4$ population. Thus, it seems likely that the questionnaire should have detected significant differences in quality of life during treatment with propionyl-L-carnitine or placebo if differences truly existed. Notable in this regard, is the fact

that the results of the present study are consistent with those of the Italian multicenter trials that evaluated the effect of propionyl-L-carnitine on quality of life by the McMaster Health Index Questionnaire (9).

Fate of claudicant limb. Previous observations indicate that intermittent claudication has a benign course in terms of local disease (21–23). In the present study, after one year follow-up, no patient required amputation, and only 2 out of 485 (0.49%) underwent surgical intervention for progression to incapacitating claudication. Critical limb ischemia (pain at rest or trophic lesions in the affected limb) occurred in 17 patients (3.5%). When considered separately, the two treatment groups showed no difference in the number of peripheral vascular events occurring during the study. Interestingly, however, the number of patients who developed pain at rest was smaller in the propionyl-L-carnitine group than in the placebo group.

In $S_1 + S_2$ population, the number of patients that at the end of study experienced a MWD improvement $\geq 50\%$ over baseline was significantly higher in the propionyl-L-carnitine group than in the placebo group. Conversely, no difference between treatments was observed in $S_3 + S_4$ population. In the overall placebo population, 71 out 166 patients who completed the study (42%) showed a MWD improvement $\geq 50\%$ after one year follow-up. This figure is in keeping with earlier studies on the natural history of intermittent claudication (24,25) but markedly higher than that of recent studies reporting improvement in walking capacity in 12% to 27% of the patients after a mean follow-up of 2.5 years (21,23). In this regard, it is conceivable that, in the setting of a formal therapeutic trial, the magnitude of the placebo effect may reflect the patient's enhanced motivation in response to the intense surveillance. This may account also for the fact that, in the present study, no patient experienced a clinically significant deterioration in walking capacity.

Laboratory findings. There were no clinically important findings on repeat electrocardiogram, biochemical or hematologic tests in either group. Furthermore, exercise-induced changes in ABPI observed at baseline were not modified by treatments.

Conclusion. For patients with mild functional impairment, the treatment of choice should be the avoidance of risk factors and the initiation of physical training. Conversely, for claudicant patients with MWD ≤ 250 m, the use of propionyl-L-carnitine will lead to a high probability of a successful and clinically relevant treatment outcome.

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