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Effects of L-Carnitine Administration on Left Ventricular Remodeling After Acute Anterior Myocardial Infarction: The L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) Trial

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Objectives. **This study was performed to evaluate the effects of L-carnitine administration on long-term left ventricular dilation in patients with acute anterior myocardial infarction.**

Background. **Carnitine is a physiologic compound that performs an essential role in myocardial energy production at the mitochondrial level. Myocardial carnitine deprivation occurs during ischemia, acute myocardial infarction and cardiac failure. Experimental studies have suggested that exogenous carnitine administration during these events has a beneficial effect on function.**

Methods. **The L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) trial was a randomized, double-blind, placebo-controlled, multicenter trial in which 472 patients with a first acute myocardial infarction and high quality two-dimensional echocardiograms received either placebo (239 patients) or L-carnitine (233 patients) within 24 h of onset of chest pain. Placebo or L-carnitine was given at a dose of 9 g/day intravenously for the first 5 days and then 6 g/day orally for the next 12 months. Left ventricular volumes and ejection fraction were evaluated on admission, at discharge from hospital and at 3, 6 and 12 months after acute myocardial infarction.**

Results. **A significant attenuation of left ventricular dilation in the first year after acute myocardial infarction was observed in patients treated with L-carnitine compared with those receiving placebo. The percent increase in both end-diastolic and end-systolic volumes from admission to 3-, 6- and 12-month evaluation was significantly reduced in the L-carnitine group. No significant differences were observed in left ventricular ejection fraction changes over time in the two groups. Although not designed to demonstrate differences in clinical end points, the combined incidence of death and congestive heart failure after discharge was 14 (6%) in the L-carnitine treatment group versus 23 (9.6%) in the placebo group (p = NS). Incidence of ischemic events during follow-up was similar in the two groups of patients.**

Conclusions. **L-Carnitine treatment initiated early after acute myocardial infarction and continued for 12 months can attenuate left ventricular dilation during the first year after an acute myocardial infarction, resulting in smaller left ventricular volumes at 3, 6 and 12 months after the emergent event.**

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Acute myocardial infarction often results in regional left ventricular dysfunction and, as a consequence, produces progressive left ventricular dilation (left ventricular remodeling) (1). Left ventricular dilation after acute myocardial infarction develops initially not only because of possible expansion of the infarcted zone (2), but also because of adaptive lengthening of noninfarcted myocardium (3). Left ventricular dilation after acute myocardial infarction can be considered a response to regional dysfunction, aimed at maintaining an adequate stroke volume despite the decline in ejection fraction.

The entity of left ventricular dilation after acute myocardial infarction, in particular end-systolic volume, represents the most powerful prognostic indicator for clinical events. Patients with larger ventricles are at higher risk of cardiac failure and death (4). It has also been demonstrated that limitation of the left ventricular dilation process after acute myocardial infarction can exert a significant clinical benefit (5). Therefore, much effort has been devoted to developing and evaluating therapeutic strategies capable of limiting left ventricular dilation after acute myocardial infarction. These show that left ventricular dilation can be modulated by 1) limiting the infarct size itself (the most important determinant of subsequent left ventricular dilation) with timely reperfusion of the infarct

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region (6); and 2) reducing left ventricular wall stress, and hence progressive left ventricular dilation of the noninfarcted region with angiotensin-converting enzyme inhibitor therapy (7–9).

Carnitine is a physiologic compound (a quaternary amine) that plays an essential role in the production of myocardial energy at the mitochondrial level. It reduces the ischemia induced increase in long-chain fatty acid concentration and thus mitigates its deleterious functional effects (10,11). Experimental and clinical studies have shown that in the ischemic (12,13), infarcted (14,15) or failing myocardium (16,17), carnitine depletion occurs rapidly. Conversely, exogenous administration can restore adequate intramyocardial carnitine levels with a suggested consequent beneficial effect on myocardial function (18–22). Because of these properties we hypothesized that early administration of carnitine after acute myocardial infarction could limit the deleterious phenomenon of progressive left ventricular dilation.

To test this hypothesis, we undertook a multicenter, randomized, double-blind, placebo-controlled study: the Carnitina, Ecocardiografia Digitalizzata, Infarto Miocardico (CEDIM) trial.

Methods

The CEDIM trial involved the intensive cardiac care units at 36 divisions of cardiology in Italy. Patients ≤80 years old with acute myocardial infarction were entered into the study if: 1) the infarct was anterior; 2) admission to the intensive care unit occurred within 24 h of onset of chest pain; 3) echocardiographic imaging of the left ventricle was of excellent quality, allowing delineation of the left ventricular contours in both end-diastole and end-systole of at least 85% of the left ventricular endocardial border; and 4) study treatment (placebo or L-carnitine) could be initiated within 24 h from onset of chest pain. A diagnosis of anterior acute myocardial infarction was made if typical chest pain lasted >30 min, with ST elevation in at least two anterior leads of ≥2 mm and not relieved by nitroglycerin. Exclusion criteria included the following: 1) a previous myocardial infarction, valvular or congenital heart disease or cardiomyopathy; 2) absence of sinus rhythm; 3) left bundle branch block; 4) conditions or concomitant diseases that could affect follow-up; 5) inclusion in another investigation.

Study design. Placebo and L-carnitine were administered in the following manner: 9 g/day, by continuous intravenous infusion, for the first 5 days, and then 6 g/day orally (2 g, three times/day) for the next 12 months. L-Carnitine or placebo was added to the standard therapeutic strategies adopted at each institution. Drugs with a direct effect on cardiac metabolism were not permitted. Because, at the time of the study onset in November 1991, the Survival and Ventricular Enlargement (SAVE) trial (7) results were not known, angiotensin-converting enzyme inhibitor therapy was not recommended and hence not systematically provided. As a result angiotensin-converting enzyme inhibitor therapy was given to only 8% of patients. However, on the basis of its proven efficacy, thrombolytic therapy was provided for 78% of patients. The study was approved by an independent ethical committee, and informed consent (either written or oral in the presence of a witness) was obtained from all patients included.

Methods of assessment. The primary end points of the trial were left ventricular volumes and ejection fraction at 12 months after the emergent event assessed by two-dimensional echocardiography. This assessment was performed at baseline (before randomization, at 11.6 ± 6.9 h from onset of chest pain) and again at discharge, as well as at 3, 6 and 12 months after acute myocardial infarction. Results are expressed as percent change for each variable. Although all available tomographic planes were obtained, only apical four- and two-chamber views were considered for volume assessment. All echocardiographic examinations were digitally recorded and sent for analysis to a central core laboratory. Real-time transfer to the core laboratory was achieved by means of a digital network whose characteristics have previously been described in detail (23). Briefly, equipment capable of converting video images into digital ones (PreVue III, Nova Microsonics) was installed in each of the 36 centers. The images were then loaded on a review station (modified 386 PC) connected to a high speed modem (Digicom SNM 32) and to a dedicated telephone line. At the core laboratory the images were received by modem and then studied on an ImageView review station (Nova) for quantitative assessment. All left ventricular volume measurements were obtained by averaging four consecutive cardiac cycles by the same observer (G.S.). The same network was used for central (24-h/day) verification of eligibility criteria and randomization of enrolled patients.

Statistical analysis. *Primary analysis.* The primary aim of the present study was to compare left ventricular ejection fraction and end-diastolic and end-systolic volumes in the two treatment arms at 12 months after randomization. Patients who, because of death or refusal, did not have the echocardiographic examination at 12 months, were excluded from the analyses. The differences were adjusted for baseline values by analysis of covariance. It has been demonstrated repeatedly (24) that the adjusted difference represents the appropriate tool for reducing variability in the outcome variable by taking into account baseline values. Baseline values were not available for 35 patients because of inadequacy of baseline echocardiographic recording or problems in digital format acquisition, or both. Baseline values were estimated using the AM procedure of BMDP statistical software (25,26). Analyses including and excluding these patients with estimated baseline values provided virtually identical results, and only the latter are presented. Analyses of patients with baseline and final values were performed according to intention to treat.

Secondary analyses. The differences, adjusted for baseline values, between the two study arms, at discharge and after 3 and 6 months, were also analyzed using analysis of covariance. As a consequence of the increasing number of deaths and withdrawals over time, different numbers of patients were included in the various analyses. Comparison of percent

change in left ventricular volume measurements between the two treatment groups were made by means of the Student *t* test for unpaired data. All p values are two-tailed. Significance was established at $p < 0.05$.

Sample size. The study was designed to detect a 5% absolute difference in left ventricular ejection fraction at 12 months between the two study arms, with an 80% power for a significance level of 0.05. On the basis of published reports, it was assumed that left ventricular ejection fraction had a standard deviation of 15%; therefore, at least 280 patients had to be recruited. However, to allow for deaths and withdrawals, and for lack of normality of outcome variables, it was decided to enroll at least 400 patients in the study.

Reproducibility. To evaluate the reproducibility of the two-dimensional echocardiographic evaluation of end-diastolic and end-systolic volumes, 30 randomly selected echocardiograms were evaluated three times by the same cardiologist who performed all the echocardiographic measurements in the CEDIM study. These echocardiograms were reexamined at random and without knowledge of the patient's identity or previous evaluation results. Variance of the three repeated measures was calculated for each subject. Intraobserver variance was estimated as the average of the values obtained for the 30 subjects. Reproducibility, expressed as standard deviation (square root of intraobserver variance), was 2.366 ml for end-diastolic volume and 2.047 ml for end-systolic volume (mean value 88.29 ml for end-diastolic volume, 45.28 ml for end-systolic volume).

All analyses were performed using BMDP statistical software for Windows and SPSS for Windows (25,27).

Results

Four hundred seventy-two patients were enrolled in the CEDIM trial: 239 patients received placebo and 233 L-carnitine; treatment was administered 12.7 ± 7.17 h after onset of chest pain. Of the 472 patients enrolled in the study, 348 were considered for analysis because they had paired echocardiograms (baseline to 12 months) available. Reasons for withdrawal of the 124 patients were as follows: 48 patients (10.1%) died; 45 (9.5%) were either lost to follow-up or refused to return for periodic control evaluation; 35 (7.4%) had an inadequate baseline echocardiogram (problems in digital procedure or poor echocardiographic quality). Baseline clinical and echocardiographic characteristics of the two treatment groups were similar and are presented in Table 1. Echocardiographic examinations were performed 11.6 ± 6.93 h after onset of chest pain. Patients considered for final analysis (n = 348) were comparable to the overall group of patients (n = 472) participating in the trial. Drug therapies prescribed at hospital discharge are given in Table 2.

Echocardiographic results. The adjusted differences for end-diastolic and end-systolic volumes and ejection fraction between the placebo and L-carnitine groups at discharge and at 3, 6 and 12 months after acute myocardial infarction are presented in Table 3. In L-carnitine–treated patients both end-diastolic and end-systolic volumes were significantly smaller at 3, 6 and 12 months after acute myocardial infarction; nonsignificant, lower end-diastolic and end-systolic volumes were also observed as early as at hospital discharge. Left ventricular ejection fraction was not significantly different in the two groups at 1 year after acute myocardial infarction.

In patients treated with L-carnitine, progressive left ventricular dilation, as shown by the percent increase in both end-diastolic and end-systolic volumes from baseline to discharge and to 3, 6 and 12 months after acute myocardial infarction, was less pronounced than that in patients treated with placebo (Table 3, Fig. 1). Left ventricular ejection fraction changes were similar in the two treatment groups during the follow-up period (Table 4).

Clinical results. Clinical events during the hospital and follow-up periods in the two treatment groups are shown in Table 5. A lower (but obviously not significantly different, because of nonappropriate study population dimension) number of deaths and fewer patients with cardiac failure after discharge were observed in the L-carnitine group than in the placebo group. The number of patients with ischemic events at follow-up was similar in the two groups of patients.

In none of the patients included in the trial did treatment have to be interrupted because of adverse events.

Discussion

Prevention of left ventricular remodeling is a major therapeutic goal after acute myocardial infarction. Several randomized, placebo-controlled trials (28–34) have clearly shown that angiotensin-converting enzyme inhibitor therapy is effective in limiting or even preventing the phenomenon of left ventricular remodeling after myocardial infarction. Differences in the degree of efficacy among various studies can be explained by different study characteristics, such as time of start of treatment after the emergent event (within hours, days or even weeks after admission to hospital), angiotensin-converting enzyme inhibitor agent or its dosage and concomitant therapies. In addition, in these studies the characteristics of enrolled patients (all patients with myocardial infarction, only anterior myocardial infarction or only those with left ventricular dysfunction as assessed by left ventricular ejection fraction) as well as the duration of treatment and consequent schedule of left ventricular evaluations in the follow-up period, influenced the reported outcome. However, even if beneficial in patients with recent myocardial infarction, angiotensin-converting enzyme inhibitor therapy has to be discontinued in some patients because of adverse events, such as symptomatic hypotension, cough, diarrhea and dizziness, all of which limit its clinical applicability.

Results of the CEDIM trial demonstrate that early and long-term administration of carnitine in patients with acute myocardial infarction is effective in attenuating progressive left ventricular dilation. Patients treated with L-carnitine had a significantly lower pronounced percent increase in both end-diastolic and end-systolic volumes than with the control group

Table 1. Baseline Characteristics by Treatment for All Randomized Patients (n = 472) and Those With Paired Echocardiographic Examinations (n = 348)

	All Patients		Patients With Paired Echo Data	
	L-Carnitine (n = 233)	Placebo (n = 239)	L-Carnitine (n = 176)	Placebo (n = 172)
Age (yr)	60 ± 11	58 ± 12	58 ± 11	56 ± 12
Gender (M/F)	195/38	204/35	150/26	151/21
History				
Hypercholesterolemia	59 (25%)	70 (29%)	50 (28%)	49 (28%)
Hypertension	97 (42%)	88 (37%)	71 (40%)	57 (33%)
Current smoker	108 (46%)	124 (52%)	84 (48%)	98 (57%)
Previous CABG or PTCA	1 (0.4%)	3 (1.2%)	—	3 (1.7%)
HR (beats/min)	81 ± 19	81 ± 16	80 ± 17	80 ± 15
SBP (mm Hg)	139 ± 25	136 ± 23	139 ± 24	136 ± 23
DBP (mm Hg)	87 ± 14	89 ± 13	87 ± 14	54 ± 14
Killip class at admission				
I	177 (76%)	182 (76%)	145 (82%)	140 (81%)
II	51 (22%)	54 (23%)	29 (17%)	32 (19%)
III	5 (2%)	2 (0.8%)	2 (1%)	—
IV	—	1 (0.2%)	—	—
Peak CK (U/liter)	1,948 ± 1,962	1,972 ± 1,816	1,944 ± 1,581	2,120 ± 1,883
Peak CK-MB (U/liter)	246 ± 310	229 ± 225	244 ± 312	265 ± 234
Thrombolysis	185 (79%)	185 (77%)	141 (80%)	138 (80%)
≤3 h	119 (51%)	125 (52%)	89 (51%)	98 (57%)
>3 h	66 (28%)	60 (25%)	52 (29%)	40 (23%)
Q wave	160 (69%)	164 (69%)	127 (72%)	123 (71%)
Time to echo (min)	737 ± 424	651 ± 405	750 ± 431	660 ± 415
EDV at admission (ml)	87 ± 24	85 ± 23	87 ± 24	85 ± 23
ESV at admission (ml)	46 ± 15	45 ± 16	45 ± 16	44 ± 16
EF (%)	48 ± 7	48 ± 7	49 ± 6	49 ± 7

Data are expressed as mean value ± SD or number (%) of patients. CABG = coronary artery bypass grafting; CK = creatine kinase; DBP = diastolic blood pressure; Echo, echo = echocardiographic, echocardiography; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; F = female; HR = heart rate; M = male; PTCA = percutaneous transluminal coronary angioplasty; SBP = systolic blood pressure.

at 3 months (end-diastolic volume 18.0 ± 2.5% vs. 11.1 ± 2.2%; end-systolic volume 22.5 ± 3.2% vs. 12.6 ± 3.1% [placebo vs. L-carnitine]), 6 months (end-diastolic volume 19.5 ± 2.3% vs. 12.7 ± 2.1%; end-systolic volume 25.5 ± 3.2% vs. 15.1 ± 9.8% [placebo and L-carnitine]) and 12 months (end-diastolic volume 28.5 ± 3.1% vs. 19.1 ± 2.7%; end-systolic volume 39.9 ± 4.2% vs. 28.9 ± 3.9% [placebo vs. L-carnitine]) after the emergent event. Also, whereas only 8% of the study patients received angiotensin-converting enzyme inhibitors, the magnitude of the carnitine effect on the echocardiographic variables was of a similar degree to that initially reported by Sharpe et al. (30) and to that observed in some ancillary echocardiographic studies of large trials (Second Cooperative North Scandanavian Enalapril Survival Study [CONSENSUS II] and SAVE) (5,34,35).

Table 2. Concomitant Therapies at Hospital Discharge

	L-Carnitine [no. (%) of pts]	Placebo [no. (%) of pts]
Digitalis	24 (10.3)	23 (9.6)
Diuretic drugs	40 (17.2)	44 (18.4)
Antiplatelet agents	163 (70)	167 (69.9)
Anticoagulant agents	65 (27.9)	63 (26.4)
ACE inhibitors	16 (6.9)	20 (8.4)
Beta-blockers	75 (32.2)	91 (38.1)
Nitrates	137 (58.8)	142 (59.4)
Calcium antagonists	59 (25.3)	56 (23.4)
Antiarrhythmic drugs	19 (8.2)	11 (4.6)

ACE = angiotensin-converting enzyme; pts = patients.

The observed effect of L-carnitine in limiting progressive left ventricular dilation after myocardial infarction can be explained by its metabolic properties and consequent functional effect. Carnitine is an essential factor in the production of energy within the myocardium: It facilitates the transport and metabolism of long-chain fatty acids, the preferred substrate for the production of metabolic energy in the heart, from the cytosol to the mitochondrial matrix where beta-oxidation occurs; moreover, it also removes compounds that are toxic to metabolic pathways. Carnitine deficiency within the myocardium can be primary or secondary to various conditions, including acute ischemia (12–15) and chronic cardiac failure (16). Experimental and clinical studies have shown that in situations characterized by its deprivation, exogenous administration of carnitine exerts a beneficial functional effect as

Table 3. Comparison of Two-Dimensional Echocardiographic Data at Hospital Discharge and During 12 Months of Follow-Up Adjusted for Baseline (recovery) Values by Means of Analysis of Covariance

	L-Carnitine (mean ± SE)	Placebo (mean ± SE)	Adjusted Difference	SE	p Value
Discharge	n = 202	n = 206			
EDV (ml)	90.9 ± 2.33	93.7 ± 2.03	−2.54*	1.790	0.15
ESV (ml)	47.8 ± 1.16	48.8 ± 1.53	−2.02*	1.334	0.13
EF (%)	48.1 ± 0.47	48.1 ± 0.52	+0.11	0.548	0.83
3 mo	n = 185	n = 179			
EDV (ml)	92.3 ± 1.67	97.2 ± 2.03	−5.35	2.299	0.02
ESV (ml)	47.8 ± 1.18	52.3 ± 1.56	−4.85	1.716	0.007
EF (%)	48.9 ± 0.49	47.4 ± 0.56	+1.42	0.676	0.03
6 mo	n = 175	n = 176			
EDV (ml)	95.5 ± 1.97	99.1 ± 2.14	−5.01	2.316	0.03
ESV (ml)	49.8 ± 0.51	53.3 ± 1.53	−4.29	1.613	0.008
EF (%)	48.4 ± 0.50	47.3 ± 0.55	+1.19	0.692	0.08
12 mo	n = 176	n = 172			
EDV (ml)	99.3 ± 2.06	105.4 ± 2.37	−7.23	2.849	0.01
ESV (ml)	55.0 ± 1.63	58.9 ± 1.75	−4.49	2.179	0.03
EF (%)	45.8 ± 0.57	45.2 ± 0.52	+0.52	0.720	0.46

*A significant negative interaction ($p < 0.05$) was present between treatment and final values. Abbreviations as in Table 1.

expressed by improved cardiac performance (18,19) and tolerance to myocardial ischemia (20–22).

The results of the CEDIM trial parallel some recent experimental observations (36) in a rat model of acute myocardial infarction. Administration of a derivative of carnitine (propionyl-carnitine) in animals, in which myocardial infarc-

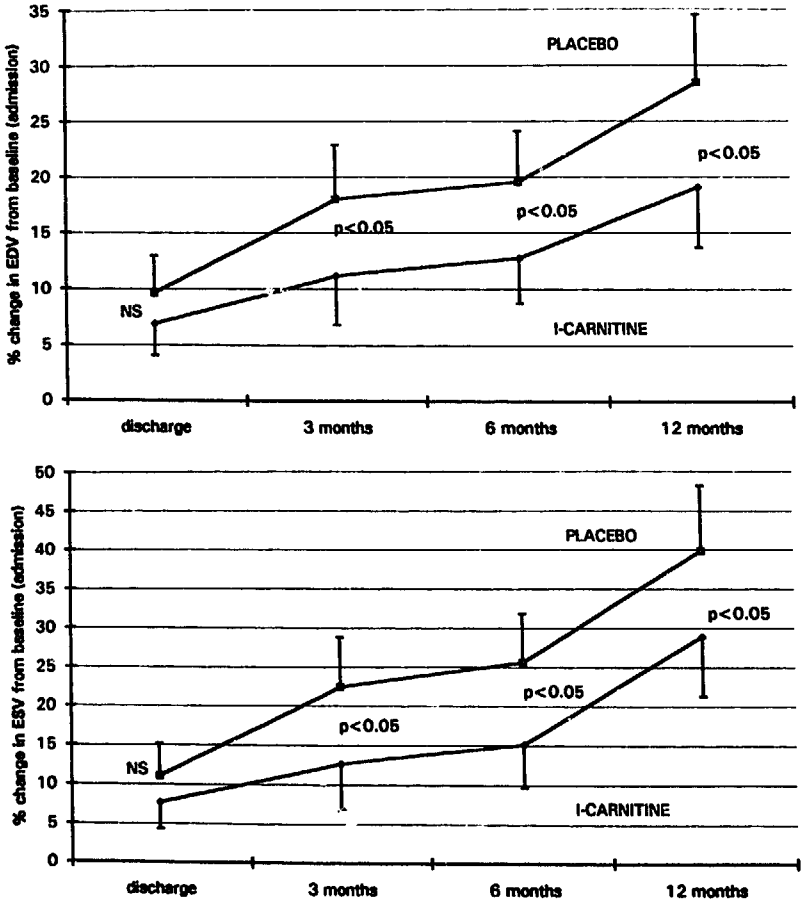

Figure 1. Percent change in end-diastolic volume (EDV) **(top)** and end-systolic volume (ESV) **(bottom)** from baseline (hospital admission) to hospital discharge (3, 6 and 12 months) in the two treatment groups (mean value ± 95% confidence interval).

Table 4. Percent Change in End-Diastolic and End-Systolic Volumes and Ejection Fraction From Hospital Admission to Discharge and at 3, 6 and 12 Months in the Two Treatment Groups

	L-Carnitine (mean ± SE)	Placebo (mean ± SE)	p Value
Discharge	n = 202	n = 206	
EDV (ml)	6.9 ± 1.4	9.6 ± 1.7	0.21
ESV (ml)	7.7 ± 1.7	11.0 ± 0.8	0.21
EF (%)	0.6 ± 0.9	0.4 ± 1.0	0.86
3 mo	n = 185	n = 179	
EDV (ml)	11.1 ± 2.2	18.0 ± 2.5	0.04
ESV (ml)	12.6 ± 3.1	22.5 ± 3.2	0.02
EF (%)	2.1 ± 1.2	−0.7 ± 1.?	0.09
6 mo	n = 175	n = 176	
EDV (ml)	12.7 ± 2.1	19.5 ± 2.3	0.02
ESV (ml)	15.1 ± 2.8	22.5 ± 3.2	0.01
EF (%)	1.01 ± 1.2	−1.9 ± 1.2	0.09
12 mo	n = 176	n = 172	
EDV (ml)	19.1 ± 2.7	28.5 ± 3.1	0.02
ESV (ml)	29.0 ± 3.9	39.9 ± 4.2	0.05
EF (%)	−5.0 ± 1.2	−5.6 ± 1.2	0.70

Abbreviations as in Table 1.

Table 5. Clinical Events During Hospital and Follow-Up Periods

	L-Carnitine [no. (%) of pts]	Placebo [no. (%) of pts]
In-hospital		
Death	11 (4.7)	14 (5.9)
Heart failure	42 (18)	38 (15.1)
Pulmonary edema	11 (4.7)	11 (4.6)
Shock	5 (2.1)	7 (2.9)
Early postinfarction angina	26 (11.1)	23 (9.6)
Reinfarction	6 (2.6)	5 (2.1)
Any of these	72 (30.9)	70 (29.3)
One-year follow-up		
Death	10 (4.3)	13 (5.4)
Heart failure	4 (1.7)	10 (4.2)
Unstable angina	21 (9)	21 (8.8)
Reinfarction	5 (2.1)	5 (2.1)
Bypass surgery	33 (14.2)	31 (13)
PTCA	23 (9.9)	24 (10)
Any of these	70 (30)	71 (29.7)

Abbreviations as in Tables 1 and 2.

tion was induced by coronary ligation, significantly decreased the magnitude of left ventricular dilation after myocardial infarction (117% in the control group vs. 36% in the group of animals treated with propionyl-carnitine). This beneficial effect on left ventricular function was similar to that observed in a third group of rats treated with enalapril (43%). It was suggested that such a beneficial effect on progressive left ventricular dilation after myocardial infarction could be due to a direct action of propionyl-carnitine on viable but jeopardized myocytes outside the infarct zone because it did not appear to alter left ventricular loading. The beneficial effect of carnitine on left ventricular remodeling after myocardial infarction can also be explained by its influence on regional left ventricular function in dysfunctioning but live myocardium surrounding the necrotic zone. In fact, it has been demonstrated (37) in an experimental model of myocardial ischemia–reperfusion that carnitine significantly reverses mechanical dysfunction both during myocardial ischemia and reperfusion. This beneficial carnitine effect on viable myocardium after myocardial infarction may have important clinical implications, because in myocardial infarction patients with viable myocardium left ventricular dilation is less pronounced than in those in whom no viable tissue could be demonstrated (38).

CEDIM trial: methodologic considerations. A significant shortcoming of the CEDIM trial is the absence of serum or urine levels of carnitine, with tissue levels for obvious reasons being impossible to obtain. Nevertheless, from other studies of experimental and clinical nature (12–17) rapid depletion of tissue and serum levels of carnitine, with increased excretion in the urine, have been demonstrated in different clinical contexts. Such deprivation can occur quite rapidly as shown by Shug et al. (12). Also, Bartels et al. (39) was able to show excess release of carnitine in the coronary sinus when heart rates were increased rapidly to ischemic conditions as shown by excessive lactate release.

Similar to other trials with analogous left ventricular functional end points, we considered, for final analysis, only patients in whom paired echocardiographic evaluations (baseline to follow-up) were available. As a consequence, patients who died or were lost to follow-up were excluded from the assessment of the final results. The possibility that the observed difference is due to bias caused by patients not included in the analyses can be ruled out by comparing the proportion of withdrawals and the reasons for withdrawal in the two groups. In contrast to the majority of studies aimed at the evaluation of therapeutic interventions after acute myocardial infarction, baseline echocardiographic evaluations in the CEDIM trial were collected very early (11.6 ± 6.9 h [mean ± SD]) after onset of chest pain and immediately before treatment and repeated upon discharge.

In the CEDIM trial, to optimize left ventricular volume evaluation accuracy and to minimize observer variability, only patients with high quality echocardiograms were admitted. Furthermore, echocardiograms were digitized and centrally evaluated in a core laboratory where a single observer reviewed and evaluated all studies. Also, all left ventricular volume evaluations were the results of the averaging of volume values obtained from four digitized cardiac cycles.

In the CEDIM trial only patients with anterior acute myocardial infarction were studied; therefore, the CEDIM results cannot be extrapolated to patients with other acute myocardial infarction locations.

Because in the CEDIM trial L-carnitine was administered at 12.7 ± 7.2 h from onset of sudden chest pain it is possible that still earlier administration might have exerted a further protective effect on ischemia–reflow dysfunction within the risk area (37). Whereas this delay in administration of treatment was contingent on the requirement for two-dimensional echo-

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cardiographic quality as an inclusion criteria, a subsequent study in which carnitine is immediately administered together with reperfusion therapy would be useful in evaluating its potential in limiting ischemic-reperfusion damage and its consequent effect on left ventricular dilation. Such a project including larger numbers of patients, aimed at establishing morbidity and mortality end points rather than functional parameters, as this study set out to achieve, is currently in preparation.

Although the present study was not designed to show any significant difference in clinical end points, the combined occurrence of death and heart failure after discharge was 14 patients in the L-carnitine–treated group versus 24 patients in the placebo group. These differences, although not significant, are consistent with a beneficial effect of the compound on the clinical events as well. It is to be noted that there were no differences in the occurrence of other clinical end points including myocardial ischemia which would reflect no action of the drug on the coronary artery system itself but only on the myocytes.

The functional benefit of L-carnitine treatment of patients with acute myocardial infarction can represent the conceptual basis for a larger scale trial specifically designed and aimed at evaluating the clinical impact of metabolic therapy of acute myocardial infarction.

Conclusions. Carnitine administration after anterior acute myocardial infarction exerts a beneficial effect on left ventricular remodeling, with a significant reduction in the increase in left ventricular volumes in the first year after acute myocardial infarction. This functional effect is observed as early as 3 months after acute myocardial infarction. It has potentially important clinical implications because, as recently demonstrated by others (5), the increase in left ventricular area (an indirect estimate of left ventricular volumes) in the first year after acute myocardial infarction is a powerful predictor of future major cardiac events. The potential clinical benefit of the administration of this naturally occurring substance (40) in patients after acute myocardial infarction needs to be verified in a larger trial with clinical end points.

The mechanism of action of carnitine on left ventricular function and remodeling is presumed to be the optimization of disturbed cellular oxidative metabolism with restoration of adequate myocardial carnitine levels.

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Appendix

*Participating Institutions and Investigators for the CEDIM Trial**

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*All cities are in Italy.

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