ABOUT carnitine

Benefits of Carnitine Use in the Ischaemic Spectrum

ABOUT PUBLISHING

ABOUTcarnitine

Benefits of Carnitine – Use in the Ischaemic Spectrum

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Summary

Introduction

Fatty acid metabolism constitutes the main source of energy for all tissues except the brain; under normal physiological conditions, in cardiac and skeletal muscle fatty acids provide the main source of energy production and account for 60–80% of all adenosine triphosphate (ATP) production. These high-energy substrates are hydrophobic and depend upon a complex process for transport across the mitochondrial membrane[1].

The first compound required for this process is L-carnitine, an essential factor in transporting long-chain fatty acids across the inner mitochondrial membrane for β-oxidation and ATP production by subsequent oxidative phosphorylation, as well as in removing toxic compounds derived from fatty acid metabolism[1,2] (*Table 1*).

L-carnitine is a naturally occurring compound that is widely distributed in nature, especially in red meats and dairy products. In normal human omnivores (non-vegetarians), approximately 75% of L-carnitine sources come from the diet while the rest (25%) is provided by endogenous synthesis from aminoacid lysine and methionine mostly in our liver and kidney[3].

L-carnitine is eliminated via urine as free carnitine and acylcarnitines, but more than 95% of all carnitine filtered in the kidney is reabsorbed by the proximal tubules, therefore maintaining the homeostatic balance of carnitine in the body[4].

Table 1. Main physiological functions of L-carnitine (adapted from[2])

Long-chain fatty acids mitochondrial transport and β-oxidation with ATP production
Removal of toxic compounds of fatty acid metabolism from the mitochondria and eventual excretion in the urine
Modulation of the mitochondrial acetyl-CoA/free CoA ratio
Stabilization of cell membranes and prevention of apoptosis

CoA=coenzyme A.

Deficiency of L-carnitine blocks the mitochondrial oxidation of fatty acids to carbon dioxide in all tissues and to ketones in the liver, and leads to lipid accumulation in the cytosol[4]. Since skeletal and particularly cardiac muscles depend on fatty acid oxidation for most of their energy, these tissues can be expected to be the most severely affected by L-carnitine deficiency[5].

In healthy people, plasma L-carnitine levels are adequately maintained by the body's own synthesis and dietary sources. However, low L-carnitine plasma levels can be primary attributable to a recessively inherited defect in muscle transport of carnitine (primary carnitine deficiency) that usually manifests itself by 5 years of age with symptoms of cardiomyopathy, skeletal-muscle weakness, and hypoglycemia[6] or secondary attributable to decreased availability of free carnitine with many causes (secondary carnitine deficiency)[6].

L-carnitine deficiency appears to also be linked to the pathogenesis of insulin resistance characterized by a cluster of associated disorders leading to atherosclerosis and cardiovascular diseases (*Figure 1*)[7,8].

From a clinical standpoint, fatty acid oxidation is impaired under L-carnitine deficiency paving the way to life-threatening alterations of skeletal and cardiac muscles[7].

Experimental and clinical studies have shown that cardiac ischemia is accompanied by a rapid depletion in myocardial L-carnitine content and a concurrent rise in free intracellular long-chain fatty acids[9,10]. L-carnitine deficiency in the failing heart has also been very well documented[11].

Heart failure (HF) is now the most common cause of mortality in developed countries. It is the final and common pathway of many types of heart disease induced by a variety of pathological insults, including hypertension, myocardial infarction and aortic stenosis. These conditions, if protracted or severe, lead to a progressive worsening of cardiac function and ultimately to heart failure[12].

Despite the beneficial effects of modern medical therapy many patients eventually progress to an advanced stage characterized by severely limiting symptoms, marked hemodynamic impairment, frequent hospitalisations and high mortality. Current medical therapies for HF are aimed at suppressing neurohormonal activation (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, β-adrenergic receptor antagonists and aldosterone receptor antagonists), and treating fluid volume overload and hemodynamic symptoms (diuretics, digoxin, inotropic agents).

These pharmacotherapies can improve clinical symptoms and slow the progression of contractile dysfunction and expansion of LV chamber volume, however they do not target the metabolic needs of the failing heart and progression can still be observed; the prognosis remains

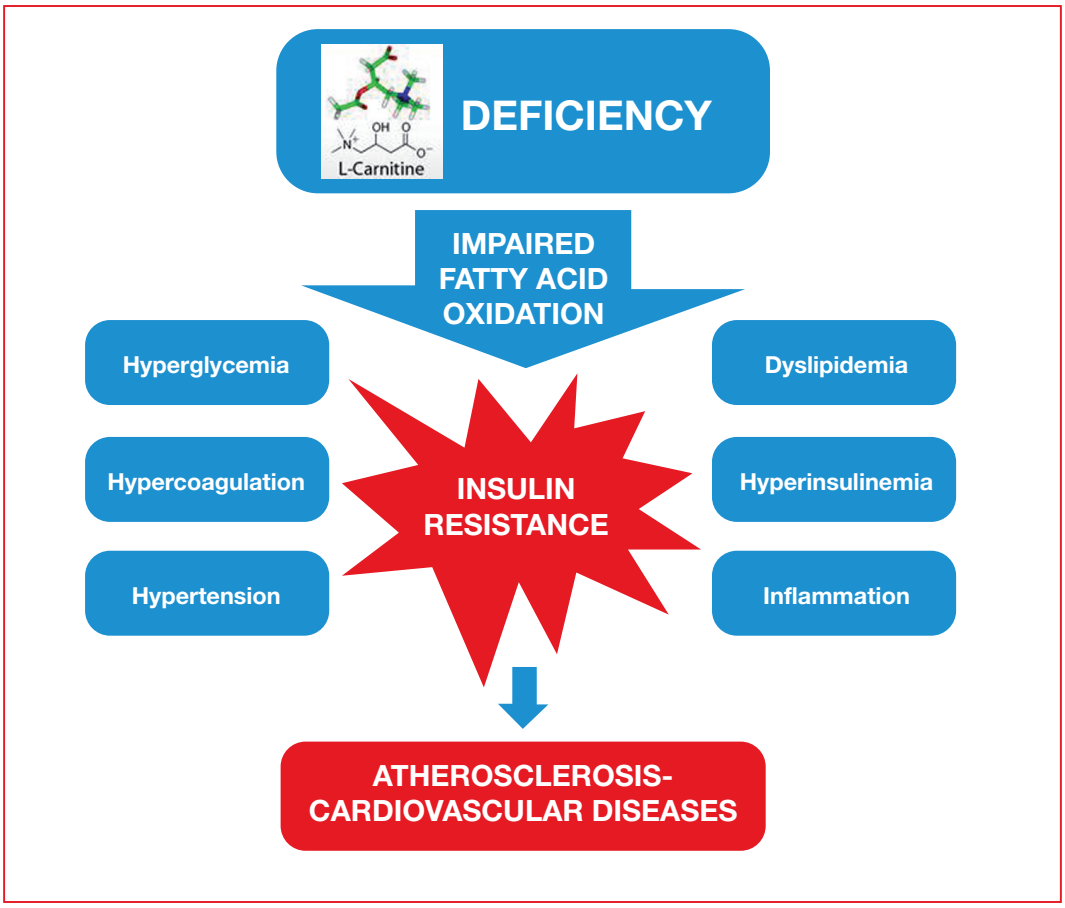

Figure 1.
L-carnitine deficiency in the pathogenesis of insulin resistance (adapted from[7,8]).

poor even for optimally treated patients[11,13]. Furthermore current treatment modalities are associated with its inherited risk and adverse events.

Under a condition like heart failure, we cannot say that the heart does not have enough "fuel" because the coronary circulation provides substrates in excess of their rate of utilization[11].

Healthy cardiomyocyte mainly uses fatty acids that enter into the cell and are converted in the mitochondria before being used by β-oxidation to produce $FADH_2$, H_2O, NADH and acetyl-CoA[14]. Once in the cytosol, fatty acids are activated and thereby bound to coenzyme A (CoA) before entering the mitochondria; the inner mitochondrial membrane is impermeable to fatty acyl-CoA molecules, and the mitochondrial uptake of fatty acyl-CoAs is thus mediated by a protein complex [(carnitine palmitoyltransferase type 1 and type 2 (CPT-1 and CPT-2), and carnitine acylcarnitine translocase (CT)] that uses carnitine as a shuttle mechanism (*Figure 2A*).

During the progression of HF, fatty acid utilization is blunted and myocardial ATP content can decrease and can drop to 60–70% of normal levels. This is accompanied by a decrease in mitochondrial oxidative metabolism and a compensatory increase in glucose uptake and glycolysis (*Figure 2B*). This altered fuel selection reflects a switch from an adult to a foetal metabolic phenotype, which may initially be a structural and metabolic adaptive response of the overloaded ventricle to maximize efficiency and decrease oxygen consumption. Over a long period of time though, this can have detrimental consequences that ultimately fail to satisfy the high energy demands of a heart coping with mechanical overload caused by an underlying disease (*Figure 2C*).

In fact, this metabolic profile is inefficient in utilizing carbon substrates for ATP production during increased energy demand as only two-thirds of the carbon found in glucose is oxidized compared with the complete oxidation of fatty acid[15,16].

So the reliance of the myocardium on glucose produces a relatively energy-deficient state that may result in decreased contractile performance[17]. Alternatively, the inability to metabolize fatty acids in the presence of excess availability may be associated with accumulation of non-oxidized toxic fatty acid derivatives, resulting in lipotoxicity[17].

This hypothesis is supported by the development of myocardial hypertrophy, HF and sudden cardiac death in children with genetic defects in myocardial fatty acid

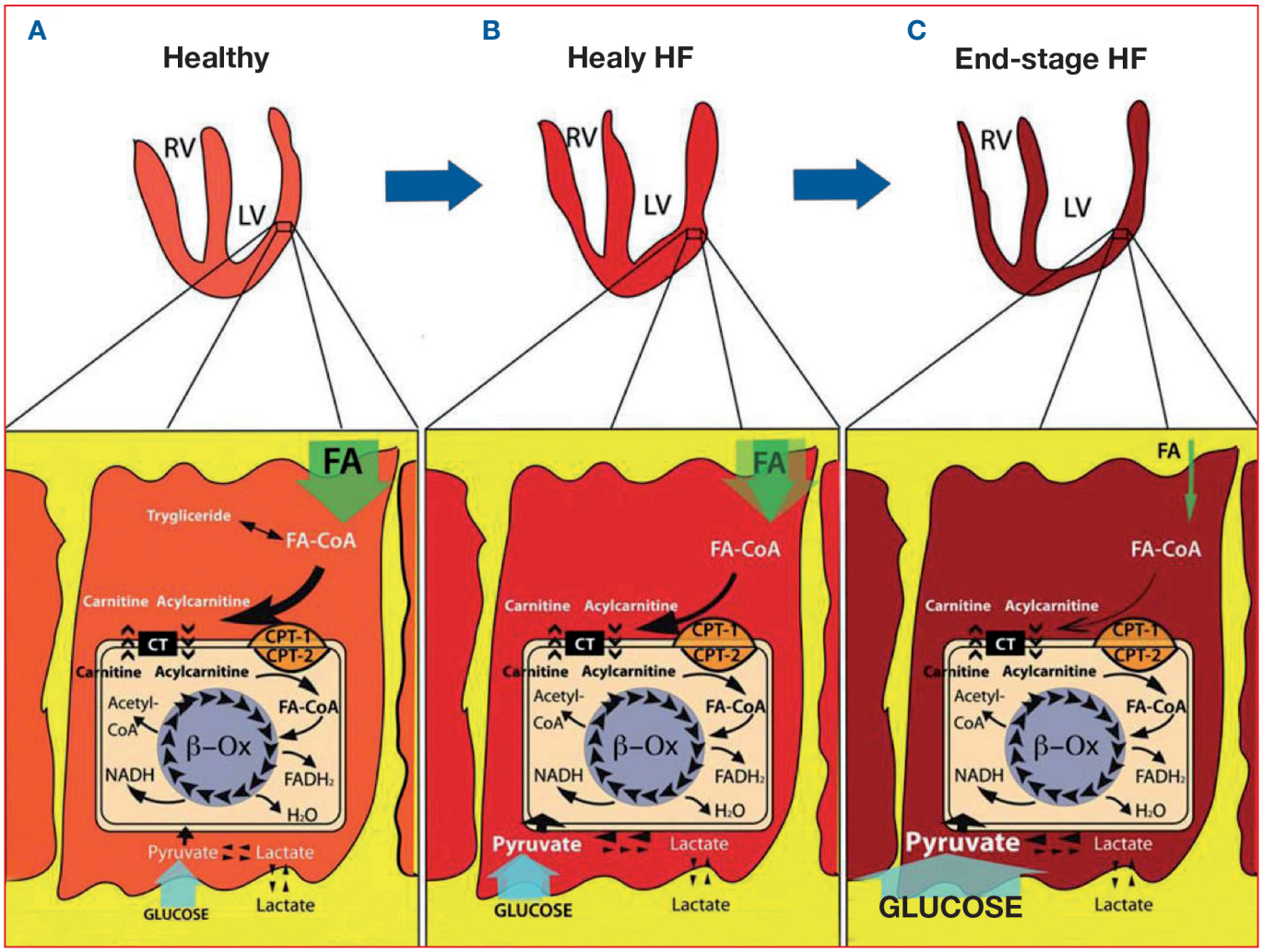

Figure 2. Cardiomyocyte substrates utilization. (A) Healthy cardiomyocyte. (B) Early HF cardiomyocyte. (C) End-stage HF cardiomyocyte. β-Ox=β-oxidation; CPT=carnitine palmitoyltransferase; CT=carnitine acylcarnitine translocase; FA=fatty acid; FA-CoA=fatty acyl-coenzyme A; $FADH_2$=reduced form of flavine adenine dinucleotide; HF=heart failure; LV=left ventricle; NADH=reduced form of nicotinamide adenine dinucleotide; RV=right ventricle (adapted from[14]).

oxidation (FAO) enzymes[18-20]. Furthermore, myocardial FAO enzyme expression is down-regulated in humans with dilated cardiomyopathy, suggesting that a gene regulatory program is responsible for the alterations in myocardial energy substrate utilization[21].

In particular, hypoxia-inducible factor (HIF)-1a and the peroxisome proliferator-activated receptor-γ (PPAR-γ), key mediators of glycolysis and lipid anabolism respectively, are jointly up-regulated in cardiac hypertrophy and cooperate to mediate key changes in cardiac metabolism that are characteristic of and contribute to common forms of heart disease. In response to pathologic stress, HIF-1a activates glycolytic genes and PPAR-γ, whose product, in turn, activates FA uptake and glycerolipid biosynthesis genes. These changes result in increased levels of lipid accumulation in hypertrophic ventricles and consequent cell death via the activation of Oct1-GADD45A-dependent caspase 3 cleavage. Therefore, the reprogramming of cardiac metabolism induced by chronic activation of the HIF-1a pathway in the heart is maladaptive, promotes cardiomyocyte apoptosis and leads, in the long term, to diminished cardiac function and progression to heart failure[12].

The importance of supporting energy metabolism in heart cells and the preservation of the mitochondria in these cells will be the focus of a new frontier in cardiovascular prevention and treatment[22]. In this context, targeting the cardiac metabolic pathways using L-carnitine may represent a suitable therapeutic intervention in the treatment of both ischemic heart disease and HF[23].

Clinical experience has shown that supplementation with L-carnitine can improve myocardial function in patients with primary systemic carnitine deficiencies. L-carnitine has also been found to exert beneficial effects in the man-

agement of cardiovascular diseases[24-28]. Several clinical studies indicate that L-carnitine supplementation can support healthy heart muscle and can significantly increase heart muscle viability. L-carnitine protects against ischemia-induced myocardial dysfunction and has been demonstrated to improve cardiac function and exercise performance, despite having no effect on myocardial oxygen requirement, in patients with angina[29-31].

In patients with chronic heart disease, administration of L-carnitine improves cardiac function and exercise performance[32,33], decreases symptoms of HF while increasing long term survival[33].

All the evidence pertinent to the therapeutic use of L-carnitine for acute myocardial infarction (AMI), summarized in a recent review, indicated that carnitine administration subsequent AMI may have the potential to reduce risk for ventricular arrhythmias and sudden cardiac death; decrease the extent of cardiac necrosis, postinfarct cardiac remodeling, and ventricular dilatation; lessen the damage to the microvasculature that often impedes restoration of appropriate cardiac blood flow following thrombolytic therapy; and improve survival (*Table 2*)[34].

The prevention of left ventricular dilatation and the preservation of cardiac function after a myocardial infarction are, indeed, clinically important, as left ventricular dilation is a powerful predictor of progression to heart failure and death[34].

Most of these results were confirmed by a meta-analysis of 13 controlled trials with a total of 3629 patients recently conducted to assess whether L-carnitine would lead to any beneficial effects on morbidity or mortality in patients who had an AMI. Compared with placebo or control, increased dietary L-carnitine is associated with a 27% reduction in all-cause mortality, a 65% reduction in ventricular arrhythmias, and a 40% reduction in angina symptoms in patients experiencing AMI[35].

Table 2. Benefits of L-carnitine administration in patients with acute myocardial infarction (adapted from[34])

Reduced risk for ventricular arrhythmias*
Decreased necrosis and infarct size
Decreased oxidative stress
Decreased ventricular remodeling
Reduced risk for angina*
Decreased risk for vascular events
Decreased mortality*

**Confirmed by meta-analysis.*

Besides its primary role in the mitochondrial oxidation of long-chain fatty acids, L-carnitine performs a second key metabolic function: the removal from the mitochondria of short and medium chain fatty acids (acetyl groups) formed as products of β-oxidation and bound to CoA as acetyl-CoA[8].

Mitochondrial accumulation of this product is toxic, inhibiting pyruvate dehydrogenase activity and glucose oxidation and has been implicated in the development of insulin resistance in skeletal muscle and heart, carnitine supplementation has gained attention as a tool for the treatment or prevention of insulin resistance and type 2 diabetes mellitus[36].

The main aim of the current collection of papers is to focus on the discussion of the experimental and clinical data supporting the beneficial effects of carnitine supplementation in patients with ischaemic heart disease.

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L-carnitine in the secondary prevention of cardiovascular disease: systematic review and meta-analysis

DiNicolantonio JJ, Lavie CJ, Fares H et al.

Mayo Clin Proc 2013;88(6):544-51

BACKGROUND AND AIM

- It is well known that during ischemic events myocardial L-carnitine levels are depleted. Targeting the cardiac metabolic pathways using L-carnitine is an alternative strategy for improving morbidity and mortality in patients who have experienced an acute myocardial infarction (AMI).
- The authors performed both a systematic review and a meta-analysis of several studies published from 1989-2007, investigating the role of L-carnitine compared to placebo or control in patients experiencing an AMI.

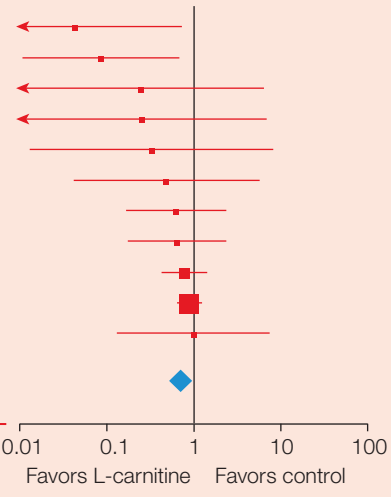
RESULTS

- Thirteen controlled trials involving a total of 3,629 patients were deemed eligible for inclusion. Each study had an average of 96 participants, with an average follow-up of 2 months (0.7-12 mo).
- In those studies, L-carnitine therapy was associated with a significant 27% reduction in all-cause mortality (OR 0.73; 95% CI 0.54-0.99; p=0.05; 11 of 13 studies) [*Figure panel A*)], a highly significant 65% reduction in ventricular arrhythmia (RR 0.35; 95% CI 0.21-0.58; p<0.0001; 5 of 13 studies) [*Figure panel B*] and a significant 40% reduction in the development of angina (RR 0.60; 95% CI 0.50-0.72; p<0.00001; 2 of 13 studies) [*Figure panel C*].

A

Study or subgroup	L-Carnitine (No.) Events	L-Carnitine (No.) Total	Control (No.) Events	Control (No.) Total	Weight (%)	Odds ratio IV, random (95% CI)
De Pasquale et al, 1990	0	49	18	97	1.2	0.04 (0.00-0.74)
Davini et al, 1992	1	81	10	79	2.1	0.09 (0.01-0.69)
Jacoba et al, 1996	0	22	1	17	0.9	0.24 (0.01-6.39)
Rebuzzi et al, 1984	0	12	1	10	0.8	0.25 (0.01-6.94)
Xue et al, 2007	0	48	1	48	0.9	0.33 (0.01-8.22)
Iyer et al, 1999	1	30	2	30	1.5	0.48 (0.04-5.63)
Singh et al, 1996	4	51	6	50	5.1	0.62 (0.17-2.36)
Kobulia et al, 2002	4	45	7	53	5.4	0.64 (0.17-2.35)
Iliceto et al, 1995	21	233	27	239	22.8	0.78 (0.43-1.42)
Tarantini et al, 2006	67	1168	75	1161	57.0	0.88 (0.63-1.24)
Rizzon et al, 1989	2	28	2	28	2.2	1.00 (0.13-7.64)
Total	**100**	**1767**	**150**	**1812**	**100**	**0.73 (0.54-0.99)**

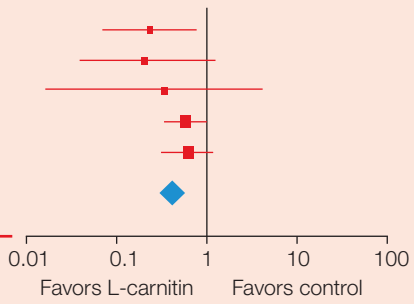
Heterogeneity: Tau²=0.01; χ^2=10.36, *df*=10 (*p*=0.41); I^2=4%
Test for overall effect: *Z*=2.00 (*p*=0.05)



B

Study or subgroup	L-Carnitine (No.) Events	L-Carnitine (No.) Total	Control (No.) Events	Control (No.) Total	Weight (%)	Risk ratio IV, random (95% CI)
Rizzon et al, 1989	2	28	13	28	13.6	0.15 (0.04-0.62)
Pehlivanoglu et al, 1996	1	12	9	18	7.1	0.17 (0.02-1.15)
Rebuzzi et al, 1984	0	12	1	10	2.8	0.28 (0.01-6.25)
Martina et al, 1992	4	12	7	8	37.2	0.38 (0.16-0.88)
Singh et al, 1996	7	51	14	50	39.3	0.49 (0.22-1.11)
Total	**14**	**115**	**44**	**114**	**100**	**0.35 (0.21-0.58)**

Heterogeneity: Tau²=0.00; χ^2=2.61, *df*=4 (*p*=0.63); I^2=0%
Test for overall effect: *Z*=4.03 (*p*<0.0001)



C

Study or subgroup	L-Carnitine (No.) Events	L-Carnitine (No.) Total	Control (No.) Events	Control (No.) Total	Weight (%)	Risk ratio IV, random (95% CI)
Singh et al, 1996	9	51	18	50	6.5	0.49 (0.24-0.99)
Davini et al, 1992	48	81	77	79	93.5	0.61 (0.51-0.73)
Total	**57**	**132**	**95**	**129**	**100**	**0.60 (0.50-0.72)**

Heterogeneity: Tau²=0.00; χ^2=0.34, *df*=1 (*p*=0.56); I^2=0%
Test for overall effect: *Z*=5.63 (*p*<0.0001)

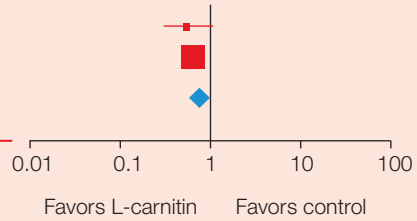


Figure. Forest plot of odds ratios for **A** all-cause mortality, **B** ventricular arrhythmia and **C** development of angina.

KEY POINTS

- The overall results of this meta-analysis support the potential use of L-carnitine in AMI and possibly in secondary coronary prevention and treatment, including angina
- Considering its low cost and excellent safety, L-carnitine should be considered in selected patients with high-risk or persistent angina after AMI who cannot tolerate pharmaceutical medicines for heart disease

L-carnitine moderately improves the exercise tolerance in chronic stable angina

Iyer RN, Khan AA, Gupta A et al.

J Assoc Physicians India 2000;48(11):1050-2

BACKGROUND AND AIM

- Evaluations of the effect of carnitine on exercise tolerance in symptomatic patients with coronary artery disease have demonstrated improvements both in exercise capacity and electrocardiographic signs of ischemia.
- In this double blind, randomized, placebo-controlled trial, the authors evaluate the safety and the efficacy of carnitine in improving exercise tolerance in patients with chronic stable angina.

MATERIALS AND METHODS

- Forty-seven patients, 30 men and 17 women, aged 56±8 years, were randomized to receive oral L-carnitine (n=28) or placebo (n=19) in the dose of 2 g/day for 3 months. The parameters assessed by computerized stress test (CST) at the beginning and the end of the trial were exercise duration, time to onset of ST changes, total ST score at peak exercise, rate-pressure product at peak exercise, and time needed for the ST changes to recover to baseline.

RESULTS

- The L-carnitine-treated group demonstrated significant improvements in exercise duration and time needed for ST changes to return to baseline (*Figure*). There was no improvement in time to onset of ST changes, total ST score at peak exercise, or rate-pressure product.
- There were no systemic adverse effects or coronary events in either group.

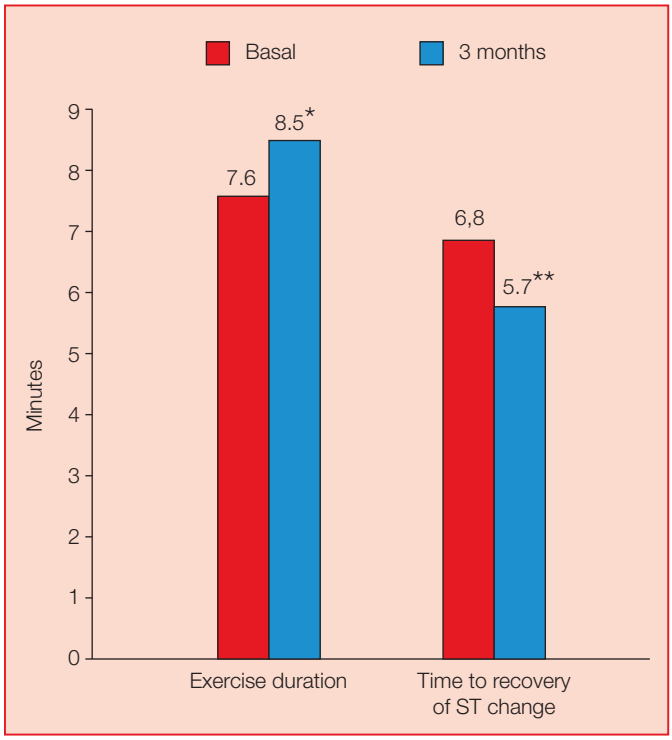


Figure. Improvement of CST parameters in L-carnitine-treated group (*p=0.006; **p=0.019).

KEY POINT

- Treatment with oral L-carnitine is safe and improves cardiac function (time to recovery of ST changes) during exercise and overall exercise performance (exercise duration) in patients with chronic stable angina

Effects of L-carnitine on exercise tolerance in chronic stable angina: a multicenter, double-blind, randomized, placebo-controlled crossover study

Cherchi A, Lai C, Angelino F et al.

Int J Clin Pharmacol Ther Toxicol 1985;23(10):569-72

BACKGROUND AND AIM

- In patients with stable effort-induced angina, the capacity for physical activity is unfortunately limited due to the onset of chest pain upon exercise. Several studies have shown that L-carnitine supplementation increases exercise tolerance and supports healthy heart function.
- In this multicenter, double blind, randomized, placebo-controlled crossover trial the authors evaluate effects of L-carnitine on exercise tolerance in patients with chronic stable angina.

MATERIALS AND METHODS

- Fifty-two male patients with chronic stable angina (abnormal cycle ergometer exercise test that induced chest pain and ST segment depression of ≥ 0.01 mV), initially entered a 10-day, single-blind, wash-out period during which all cardioactive drugs were withdrawn and placebo was administered. They were then randomized to receive either placebo or 1 g of L-carnitine twice daily, for 4 weeks. At the end of this phase, patients crossed over to the alternative therapy for another 4 weeks.

RESULTS

- In 44 of the original 52 patients that completed the trial, L carnitine significantly increased the maximum exercise workload tolerated, the watts to onset of angina and decreased ST segment depression (electrocardiographic evidence of ischemia) both at the maximum workload and at the maximum workload common to the active drug and placebo (*Figure*).
- 22.7% of patients taking L-carnitine self-reported resolution of anginal episodes, compared with 9.1% in the placebo group.

KEY POINT

- **Short-term treatment with L-carnitine in patients with angina pectoris has a beneficial effect on exercise-induced angina and objectively modifies the ECG indices of myocardial ischemia**

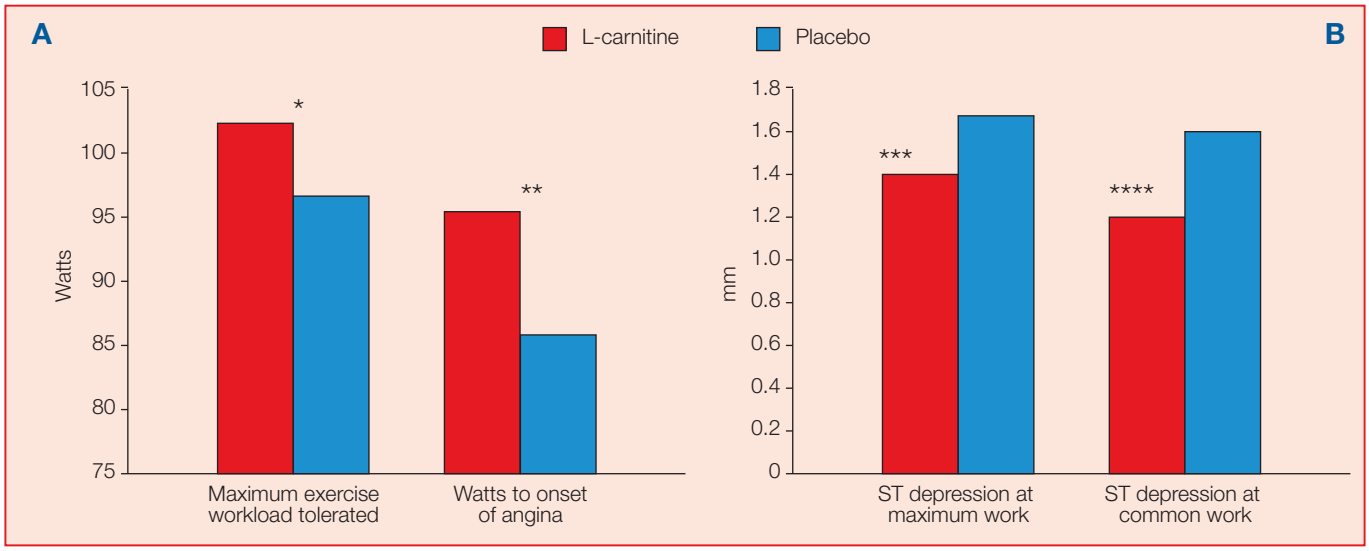


Figure. Mean changes of **A** maximum exercise workload tolerated, watts to onset of angina and **B** ST segment depression both at the maximum workload and at the maximum workload common in L-carnitine and placebo groups (*p=0.001; **p=0.000; ***p=0.05; ****p=0.005).

The therapeutic effect of L-carnitine in patients with exercise-induced stable angina: a controlled study

Cacciatore L, Cerio R, Ciarimboli M et al.

Drugs Exp Clin Res 1991;17(4):225-35

BACKGROUND AND AIM

- Due to its intrinsic metabolic and cardioprotective effects, particularly during myocardial ischaemia, L-carnitine is a drug of great interest both as a single drug therapy or in association with other traditionally used agents.
- The aim of this study was to investigate the cardioprotective and metabolic effects of L-carnitine in patients with stable, exercise-induced angina who were receiving other cardiovascular therapies.

MATERIALS AND METHODS

- This study was performed at three different centres and included 200 patients (62.5 male), 40 to 65 years of age, suffering from exercise-induced stable angina for at least one year and having ischaemic attacks characterized by classical onset and complete regression following rest or the administration of sublingual nitroglycerine. In 100 randomly selected patients, L-carnitine was administered orally in daily doses of 2 g in addition to the already instituted therapy, and the effect studied over a 6-month period. The remaining 100 patients formed the control group.

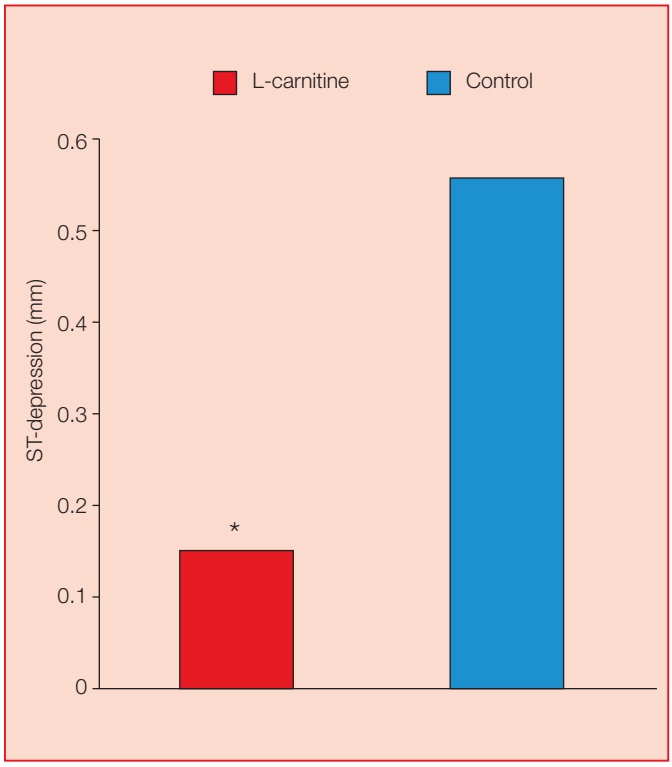


Figure 1. Reduction in ST-segment depression over a 6-month of L-carnitine treatment (*p<0.0001).

RESULTS

- Supplementing conventional medical therapy with L-carnitine for 6 months significantly reduced the incidence of premature ventricular contractions and also improved exercise tolerance as evidenced by reduction in ST-segment depression (*Figure 1*).
- Compared to the control group, L-carnitine group showed a significant reduction of exercise-induced electrocardiographic signs of ischaemia. In addition, a concomitant increase in the number of patients belonging to class I of the NYHA (New York Heart Association) classification, a proportional reduction in those belonging to class II and a reduction in the consumption of cardioactive drugs (*Figure 2*) have been reported at the end of the study in L-carnitine-treated group.
- Patients receiving L-carnitine also showed a significant reduction in total cholesterol and triglyceride levels (*Figure 3*).

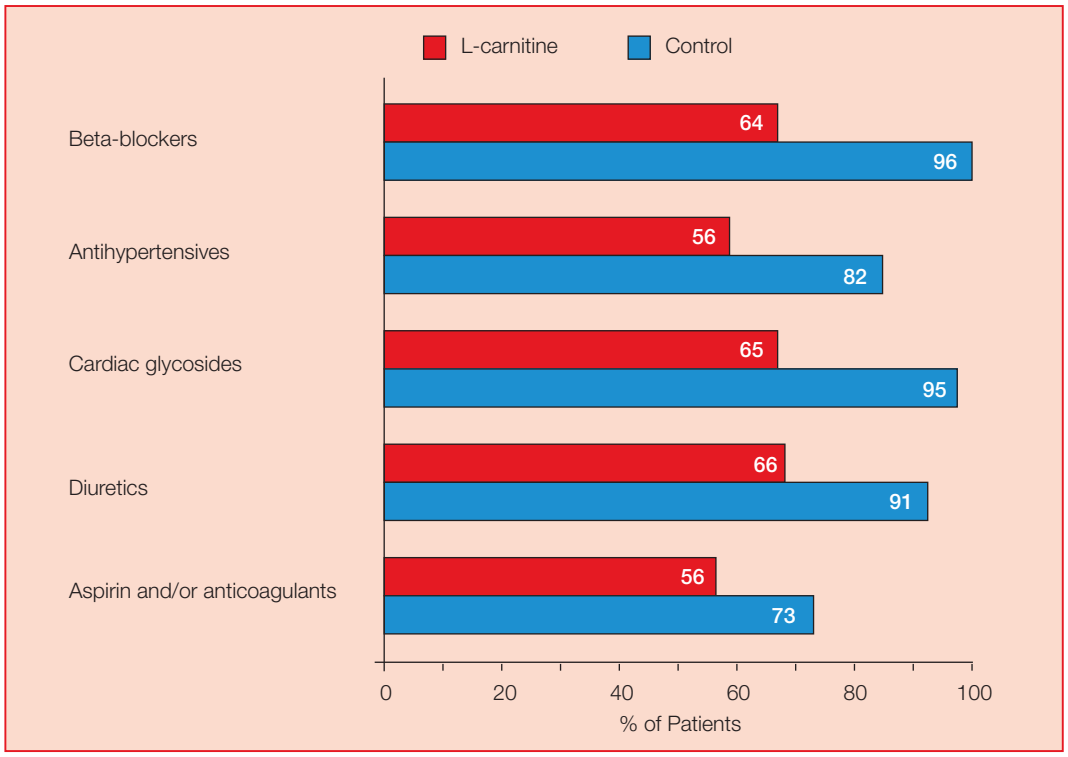


Figure 2.
Consumption of beta-blockers, antihypertensives, cardiac glycosides, diuretics, aspirin and/or anticoagulants at the end of trial in the two groups.

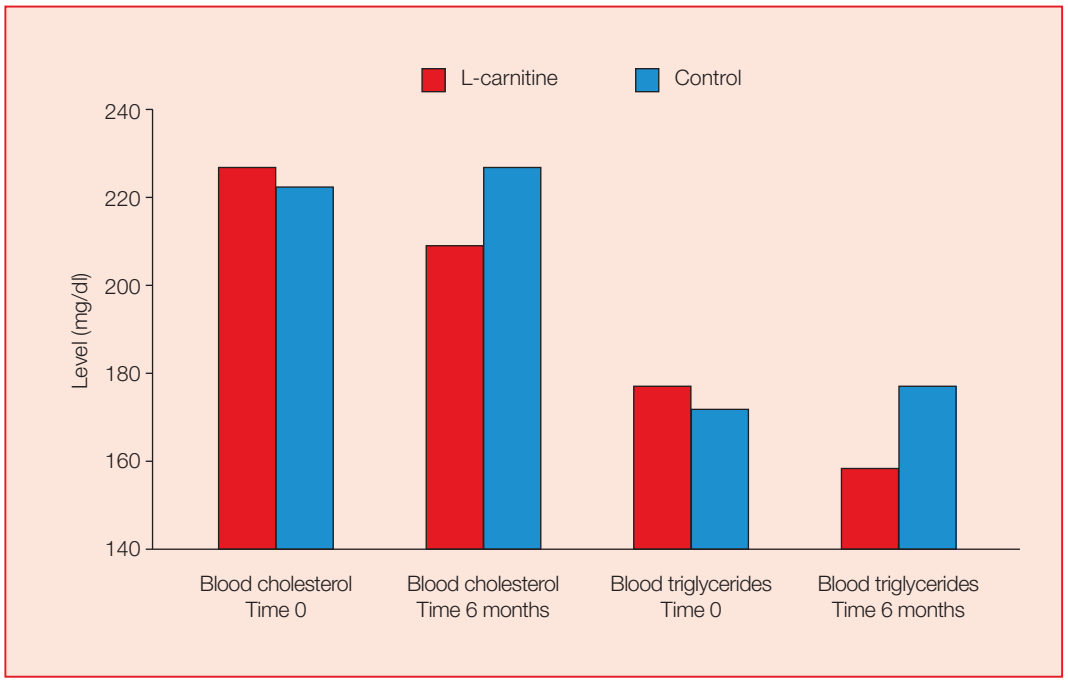


Figure 3.
Cholesterol and triglyceride levels in the L-carnitine and control groups, before and after treatment with L-carnitine.

KEY POINTS

- Patients with exercise-induced stable angina showed significant and progressive improvement in cardiac function during the 6 months following the addition of 2 g of L-carnitine to their therapeutic regimen
- L-carnitine use was also associated with a significant reduction in the consumption of all other cardiovascular therapies
- The results of this study indicate that L-carnitine is able to exert cardioprotective effects in patients with angina and improves the metabolic functioning of the myocardium

L-carnitine treatment in patients with mild diastolic heart failure is associated with improvement in diastolic function and symptoms

Serati AR, Motamedi MR, Emami S et al.

Cardiology 2010;116(3):178-82

BACKGROUND AND AIM

- In patients with diastolic heart failure, despite normal contractility, cardiac output cannot increase without a compensatory elevation of ventricular filling pressure due to impaired relaxation (a highly energy-dependent process requiring ATP). As an important component of fatty acid transfer into the mitochondria for β-oxidation and ATP production, L-carnitine plays an important role during diastolic relaxation.
- In this double blind, randomized trial the authors evaluate the effects of L-carnitine on patients with a history of mild heart failure and diastolic dysfunction.

MATERIALS AND METHODS

- A total of 60 patients with a history of NYHA (New York Heart Association) functional class II symptoms and ejection fraction >45% with documented grade 1 diastolic dysfunction on echocardiogram were randomized to oral L-carnitine supplementation at a dose of 1.5 g per day for 3 months (n=29) versus placebo (n=30). Echocardiographic and follow-up measurements of diastolic parameters were assessed at baseline and after the end of the study.

RESULTS

- Oral L-carnitine supplementation showed significant improvement in the left atrial size, septal e lateral mitral E′ velocities and isovolumic relaxation time (*Table*).
- Dyspnea also significantly improved in L-carnitine treated patients.

Table. Echocardiographic data before (baseline) and after 3 months in the L-carnitine group

Variables	Baseline	3 month after L-carnitine	p value
Left atrial size, cm	3.6±0.4	3.4±0.5	0.01
Isovolemic relaxation time, ms	127±26	267±58	0.007
Mitral E′ septal velocity, m/s	0.064±0.011	0.074±0.018	0.013
Mitral E′ lateral velocity, m/s	0.082±0.017	0.091±0.02	0.006

KEY POINT

- **In patients with mild diastolic heart failure, 3 months treatment with oral L-carnitine showed improvement in some important indices of diastolic parameters together with improvement in symptoms**

Serum free carnitine levels in children with heart failure

Ergür AT, Tanzer F, Cetinkaya O.

J Trop Pediatr 1999;45(3):168-9

BACKGROUND AND AIM

- Carnitine availability becomes a limiting step for β-oxidation in certain physiological and pathological diseases and carnitine supplementation enhances fatty acid metabolism in the mitochondria, restoring normal mitochondrial function by maintaining the equilibrium between acyl-CoA and free CoA.
- The aim of this study was to estimate the serum free carnitine (SFC) levels in children with heart failure (HF) and healthy controls, and to study the effect of L-carnitine administration.

MATERIALS AND METHODS

- This study was carried out on 91 children admitted with a diagnosis of HF and on a control group consisting of 30 healthy children (20 girls, 10 boys). Of the 91 patients with HF, 24 were administered 50 mg/kg oral L-carnitine for a period of 15 days.

RESULTS

- The mean SFC levels of the patients with HF were significantly lower than those of the control group (*Figure A*).
- After L-carnitine administration, mean SFC levels of 24 patients increased significantly (*Figure B*).

KEY POINT

- The results of this study indicate that carnitine deficiency is present in children with HF and administration of L-carnitine helps recovery

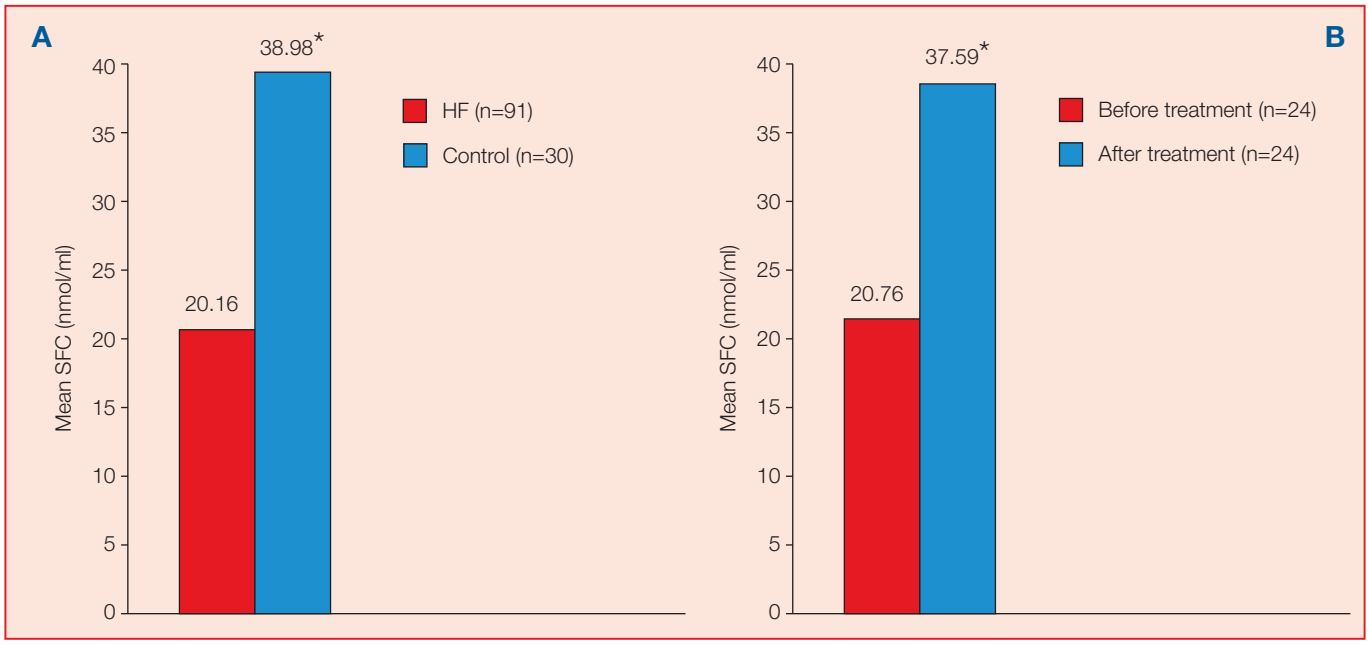


Figure. A Mean serum free carnitine (SFC) levels of children with heart failure (HF) and healthy controls. **B** Mean SFC levels before and after L-carnitine treatment (*p<0.01).

Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: the L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) Trial

Iliceto S, Scrutinio D, Bruzzi P et al.

J Am Coll Cardiol 1995;26(2):380-7

BACKGROUND AND AIM

- In the months following an acute myocardial infarction (AMI), the left ventricle often enlarges, and the pumping action of the heart becomes less efficient. Some evidence suggests that L-carnitine can help prevent ventricular remodeling.
- This multicenter, double-blind, randomized, controlled trial evaluate the effects of L-carnitine administration on long-term left ventricular dilation in anterior AMI patients.

MATERIALS AND METHODS

- A total of 348 patients who met the inclusion criteria (anterior infarct, admitted and treated within 24 hours of symptom onset, echocardiographic data available) were randomized to receive placebo (n=172) or L-carnitine (n=176) 9 g/day by continuous IV infusion for the first 5 days, then 2 g thrice daily orally (6 g/day) for 12 months. The primary study endpoint was the change in left ventricular volumes and ejection fraction (EF) at 3, 6 and 12 months following AMI.

RESULTS

- Although there was no change in overall EF, both end-diastolic and end-systolic volumes were significantly smaller at 3, 6 and 12 months post-infarction in L-carnitine group (*Figure*).

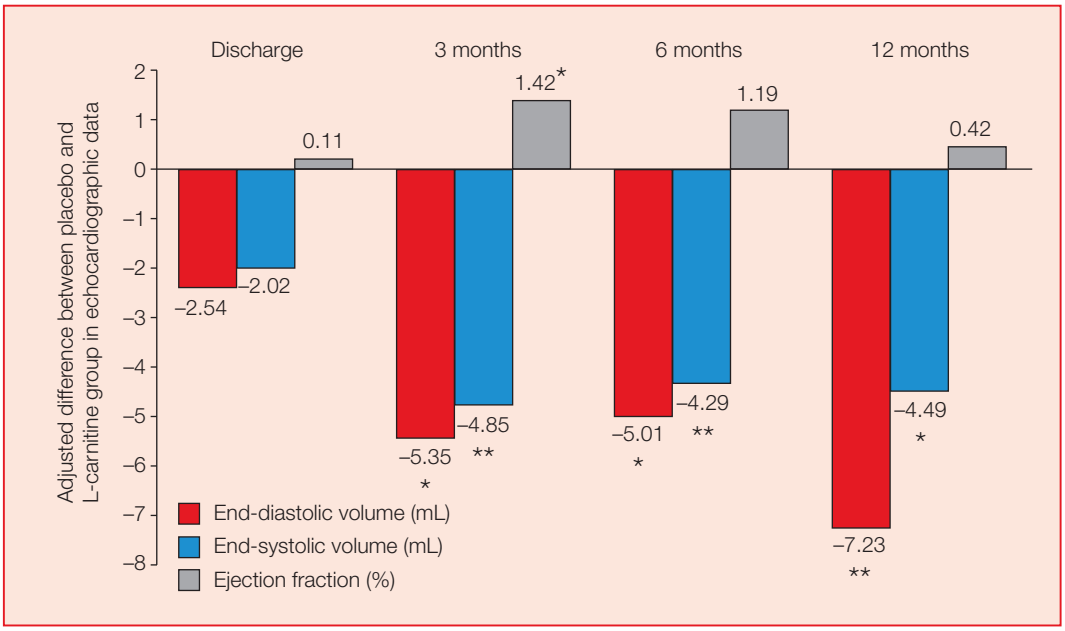


Figure.
Between-group difference (placebo minus L-carnitine) in values of 3-dimensional echocardiographic data at various timepoints, adjusted for baseline (recovery) values (*p≤0.03; **p≤0.01).

KEY POINT

- **This large multicenter, randomized, double-blind, clinical trial suggests that the early and long-term administration of L-carnitine attenuates progressive left ventricular dilatation during the first year after an AMI**

Metabolic treatment with L-carnitine in acute anterior ST segment elevation myocardial infarction. A randomized controlled trial

Tarantini G, Scrutinio D, Bruzzi P et al.

Cardiology 2006;106(4):215-23

BACKGROUND AND AIM

- The results of the multicenter, randomized, double-blind Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) trial suggest that the early and long-term administration of L-carnitine attenuates progressive left ventricular dilatation.
- Based on these results, it was hypothesized that its administration could improve clinical status and survival in patients with anterior AMI. To verify this hypothesis, the CEDIM 2 multicenter trial was undertaken.

MATERIALS AND METHODS

- A total of 2,330 patients with acute MI were randomized to receive either placebo (n=1,162) or L-carnitine (n=1,168) 9 g/day IV for 5 days followed by oral administration of 4 g/day for 6 months, added to standard therapeutic therapy adopted to each of 153 participating centers. The primary endpoint was a composite of death and heart failure at 6 months; 5-day mortality was the secondary endpoint.

RESULTS

- During the 6-month follow-up, the primary endpoint was not significantly lower by 12% in the L-carnitine group than in the placebo group (9.2% versus 10.5%; p=0.27).
- Mortality at 5 days from randomization was significantly reduced in L-carnitine group compared to placebo group (p=0.041). The difference in mortality decrease in the following period with mortality rate from day 7 to day 180 was similar in the two groups (*Figure*).

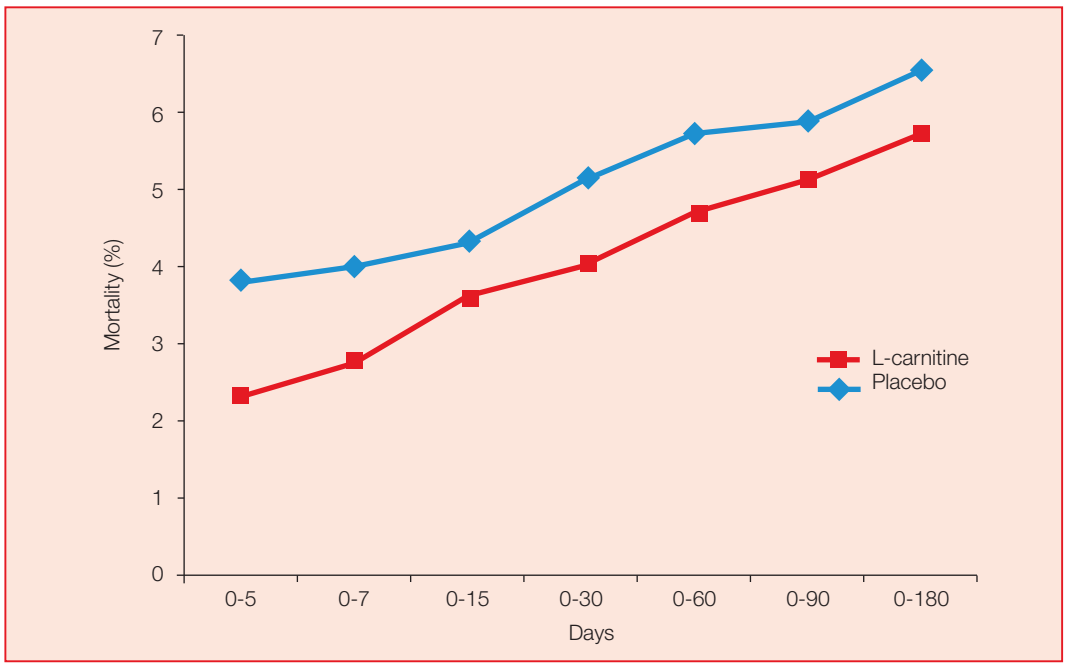


Figure.
Cumulative mortality at various times from randomization (*p=0.041).

KEY POINT

- Administration of L-carnitine as soon as possible after the acute event led to a reduction in early mortality without affecting the risk of death and heart failure at 6 months

Effects of carnitine on 6-month incidence of mortality and heart failure in patients with acute myocardial infarction

Kobulia B, Chapichadze Z, Andriadze G, Machavariani P

Ann Biomed Res Educ 2002;2(3):240-3

BACKGROUND AND AIM

- Targeting the cardiac metabolic pathways using L-carnitine is an alternative strategy for improving morbidity and mortality in patients who have experienced an acute myocardial infarction (AMI).
- The aim of this study was to compare L-carnitine treatment with standard therapy in patients with AMI.

MATERIALS AND METHODS

- In this phase III, multicenter, randomized, double-blind, placebo-controlled trial, 98 patients with AMI were randomly assigned to L-carnitine (n=45) and control (n=53) group. L-carnitine was administered for 6 months (at a dose of 9 g/day intravenously for the first 5 days and then 4 g/day orally to the 180th day). The primary endpoint was 30-day mortality and re-infarction during 96 hours of hospitalization.

RESULTS

- Compared with control group, the number of patients who died by 6 months was less in the L-carnitine group (12.3% vs 9.7% respectively, $p<0.05$). Treatment with L-carnitine also reduced the rate of re-infarction during hospitalization and heart failure complications after 6 months by 15,7%.

KEY POINT

- **L-carnitine use is associated with a lower 6-month mortality, re-infarction rate and number of heart failure complications in patients after AMI**

Anti-arrhythmia treatment using L-carnitine in acute myocardial infarct

Martina B, Zuber M, Weiss P et al.

Schweiz Med Wochenschr 1992;122(37):1352-5

BACKGROUND AND AIM

- L-carnitine in high doses has been postulated to have an anti-arrhythmic effect and this has also been clinically proven.
- This small, double-blind study investigated the anti-arrhythmic effects of L-carnitine when given to patients with acute myocardial infarction (AMI) 4-12 hours after onset of pain.

MATERIALS AND METHODS

- Twenty patients with AMI who presented within 4 to 12 hours after the onset of pain were included. Patients were randomized to L-carnitine 5 g (n=12) or placebo (n=8) at hours 0, 12, 24, 36, and to 2–3 g on days 3 to 7 by intravenous infusion over 2 hours. The 2 groups were similar for age, gender, infarct site, maximum CPK and conventional anti-arrhythmic therapy at baseline.

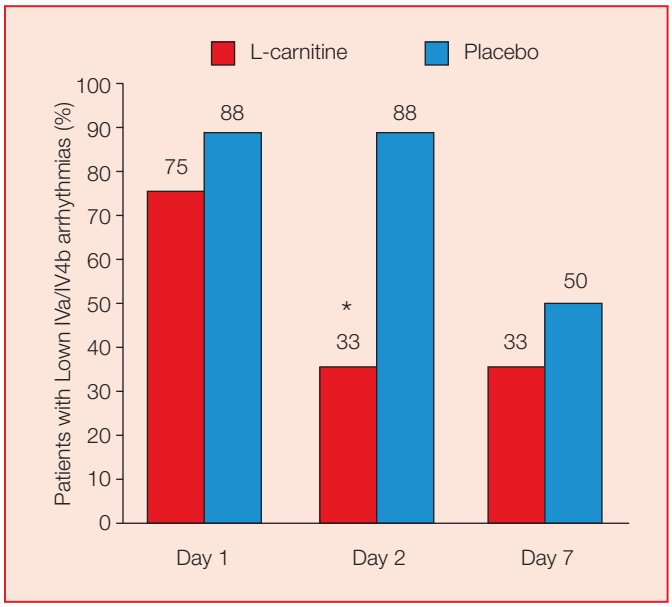


Figure. Incidence of high-grade arrhythmias in the L-carnitine and placebo groups (*p<0.05).

RESULTS

- 24-hour Holter-ECG was performed on days 1, 2 and 7 and showed no significant difference between the two groups with respect to incidence of premature ventricular beats (PVB) per hour.
- On day 2 following AMI, only 4 of 12 carnitine-treated patients (33%) experienced high-grade arrhythmias (Lown class IVa and IVb) compared to 7 of 8 patients (88%) in the placebo group (*Figure*). This difference is significant: p=0.028 (Fisher's exact test).
- High-dose L-carnitine therapy was well tolerated.

KEY POINT

- **The results of this study suggest that L-carnitine in high doses was well tolerated and was associated with significantly lower incidence of high-grade arrhythmias on the second day following AMI**

A randomised, double-blind, placebo-controlled trial of L-carnitine in suspected acute myocardial infarction

Singh RB, Niaz MA, Agarwal P et al.

Postgrad Med J 1996;72(843):45-50

BACKGROUND AND AIM

- Clinical studies have shown that myocardial ischaemia is associated with a reduction of free L-carnitine resulting in long-chain acylcarnitine accumulation and cardiac necrosis due to over production of reactive oxygen species.
- This study evaluated the effect of L-carnitine administration on cardiac enzymes and lipid peroxides in patients with suspected acute myocardial infarction (AMI).

MATERIALS AND METHODS

- In this randomized, double-blind, placebo-controlled trial, the effects of the administration of oral L-carnitine (2 g/day) for 28 days were compared in the management of 51 (carnitine group) and 50 (placebo group) patients with suspected AMI. Clinical, electrocardiographic, radiologic and laboratory data were obtained for all patients during hospitalization.

RESULTS

- L-carnitine supplementation reduced the mean infarct size as assessed by cardiac enzymes (creatine kinase, creatine kinase MB) activity and improved QRS-score (*Figure 1*). In addition, there were a greater reduction of serum aspartate transaminase and a smaller rise of serum lactate dehydrogenase in the L-carnitine group indicating lower cardiac necrosis compared to placebo (*Figure 2*). Lipid peroxides also showed significant reduction in the carnitine group ($p<0.05$).
- The incidence of angina, total arrhythmias, total cardiac events and non-fatal infarction was significantly lower in the L-carnitine group versus the placebo group during the 28 days of follow-up ($p<0.05$) [*Figure 3*].

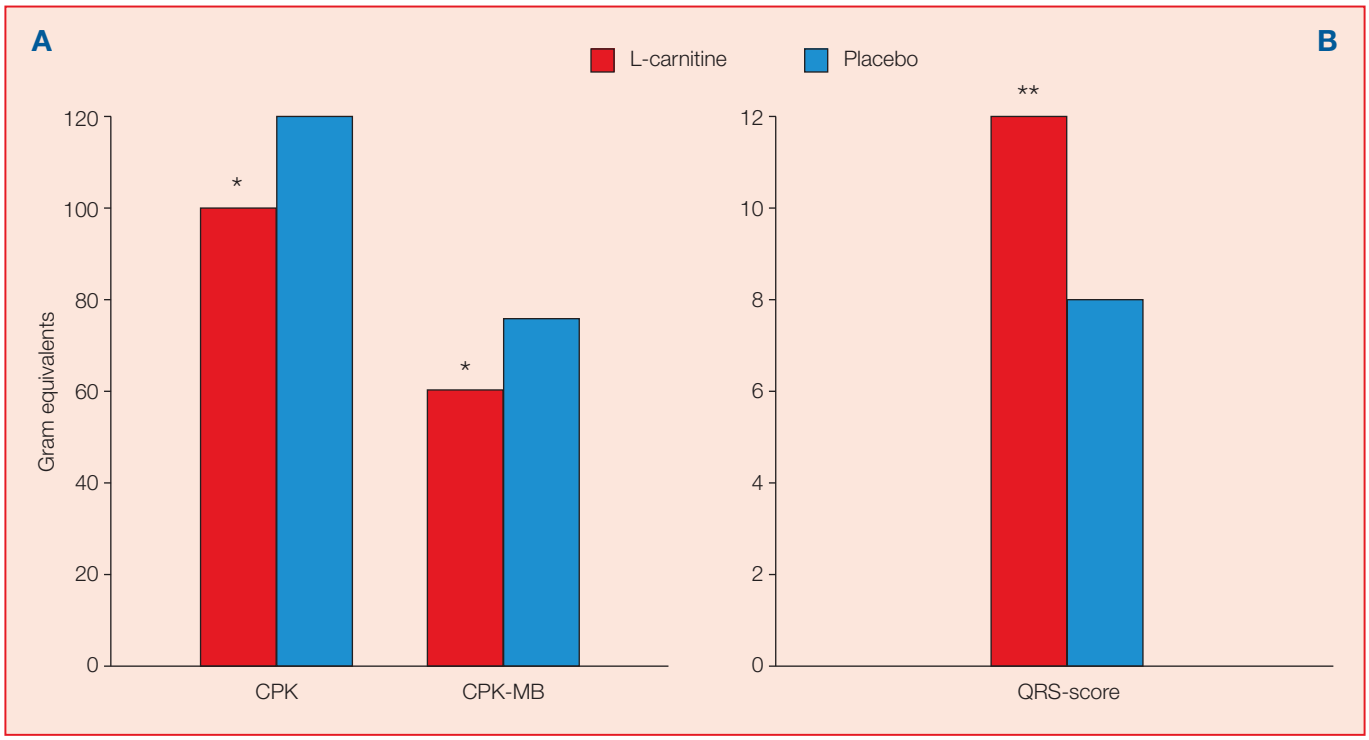


Figure 1. A Size of necrosis assessed by creatine kinase (CPK) and creatine kinase MB (CPK-MB) levels and **B** QRS-score in L-carnitine and placebo groups (*$p<0.05$; **$p<0.01$). Values are mean.

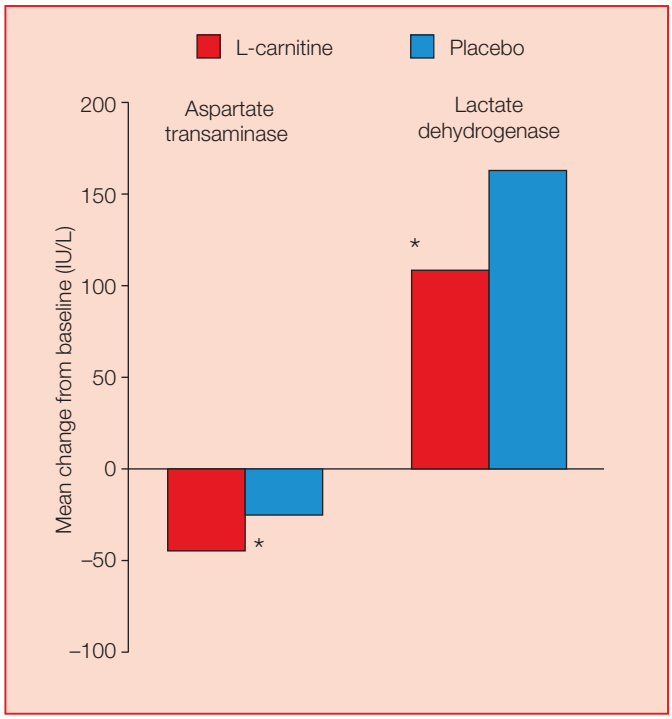


Figure 2.
Effect of carnitine treatment on aspartate transaminase and lactate dehydrogenase (*p<0.05).

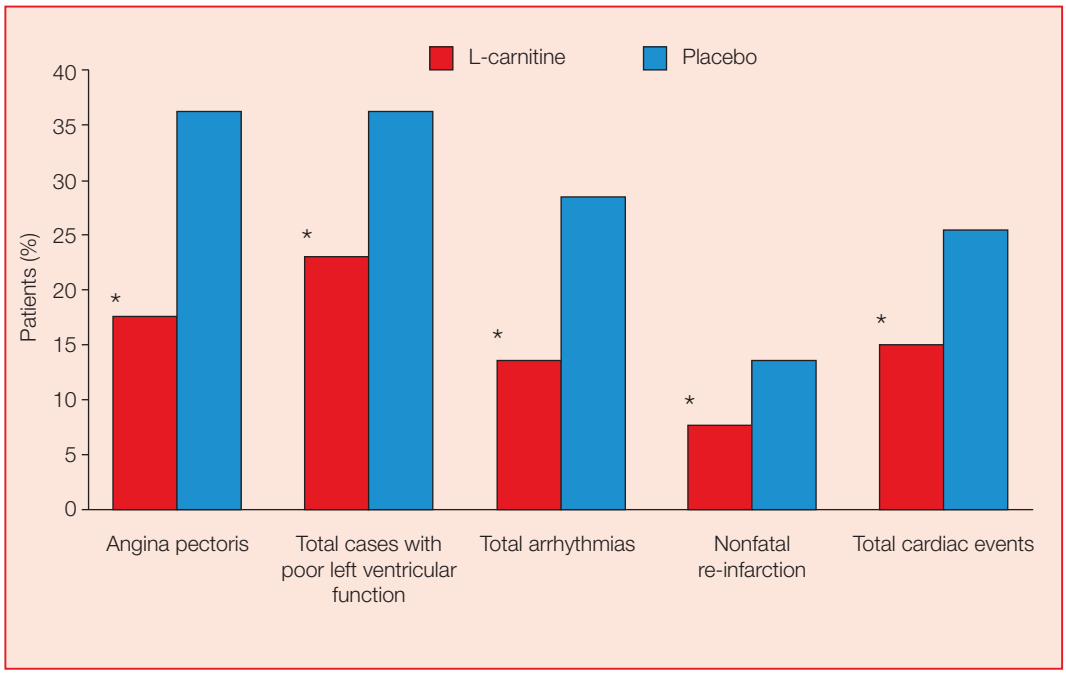


Figure 3.
Adverse events in L-carnitine and placebo groups at 28 days of follow up (*p<0.05).

KEY POINTS

- In AMI, the ischemic damage and metabolic reactions are so rapid that benefits of treatment are difficult to achieve if treatment is not given immediately after infarction
- When administered acutely, L-carnitine supplementation offers protection against cardiac necrosis and AMI complications

High doses of L-carnitine in acute myocardial infarction: metabolic and antiarrhythmic effects

Rizzon P, Biasco G, Di Biase M et al.

Eur Heart J 1989;10(6):502-8

BACKGROUND AND AIM

- The fatty acid esters that accumulate as a result of impairment of fatty acid oxidation in carnitine-deficient states may be arrhythmogenic under certain conditions.
- The aim of this study was to assess whether high-dose L-carnitine increases the production and urinary excretion of acylcarnitine, and whether it can reduce early ventricular arrhythmias, in patients with acute myocardial infarction (AMI).

MATERIALS AND METHODS

- In this double-blind trial, 56 patients with AMI were randomly assigned to receive L-carnitine (n=28) IV (100 mg per kg body weight every 12 hours for a total of 36 hours) or placebo (n=28). Concentrations of free carnitine, short chain acylcarnitine esters and long chain acylcarnitine esters in serum and urine were measured. Blood samples for carnitine assays were also taken from 28 healthy control subjects for comparison.

RESULTS

- On the second day of treatment, compared to placebo, L-carnitine reduced the number of episodes of ventricular tachycardia by 80% ($p<0.05$), the number of ventricular premature beats by 80% ($p<0.05$), and significantly reduced the amount of time with multiform or paired ventricular premature beats (*Figure*). These anti-arrhythmic effects were accompanied by significant increases in serum and urinary levels of free L-carnitine confirming L-carnitine absorption and reflecting the impact of supplementation.
- Elimination of both free and total carnitine was significantly higher in placebo recipients compared with the healthy control group.

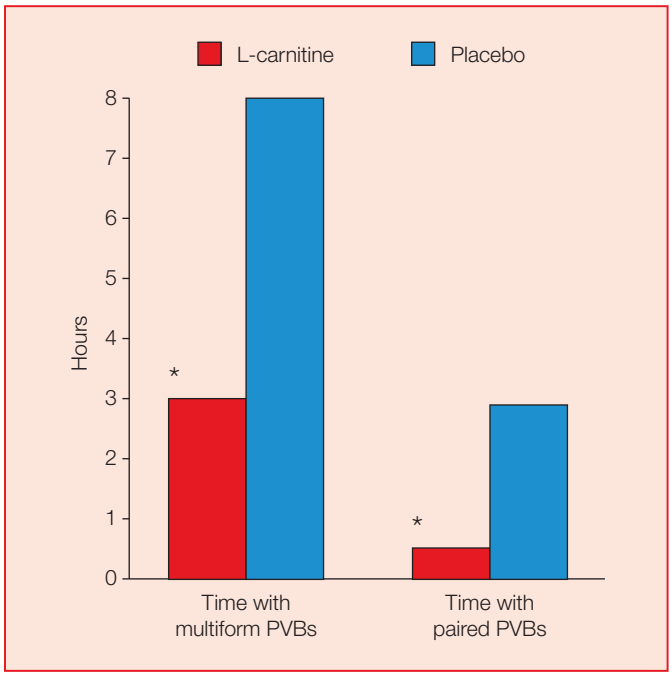


Figure. Time with multiform or paired premature ventricular beats (PVBs) in the placebo and L-carnitine groups (*$p<0.01$).

KEY POINTS

- Compared with normal subjects, patients with AMI experience significant increases in serum carnitine within the first 48 hours after the event. The urinary excretion of both free and total carnitine is also significantly increased during this time period
- Administration of high-dose L-carnitine following AMI significantly increases levels of carnitine esters in both serum and urine
- The elimination of acyl compounds in excess exerted by L-carnitine may account for the reduction in ventricular arrhythmias observed on the second day in the high-dose L-carnitine group compared to the placebo one

Beneficial effects of L-carnitine in the reduction of the necrotic area in acute myocardial infarction

Rebuzzi AG, Schiavoni G, Amico CM et al.

Drugs Exp Clin Res 1984;10:219-23

BACKGROUND AND AIM

- Abnormal elevations in the serum concentrations of cardiac enzymes may be the key diagnostic element for the prognosis of mortality and complications in acute myocardial infarction (AMI). L-carnitine administration may be useful for limiting necrotic damage during ischaemia, and serum enzyme levels may be a surrogate marker for such damage.
- This study assesses the effect of orally administered L-carnitine on the extent of the necrotic area in patients with AMI.

MATERIALS AND METHODS

- A total of 22 patients (77% males) hospitalized for AMI were studied. L-carnitine was administered (40 mg/kg/die for the first 5 days of hospitalization) as an adjunct to standard therapy in 12 AMI patients within 8 hours of the onset of chest pain. The next 10 patients, who received standard therapy alone, served as a control group. Samples of blood were taken from all patients at the moment of hospitalization and every 4 hours up to 48-72 hours. Necrotic area extent was measured by CPK-MB enzyme release.

RESULTS

- Both mean and maximum CPK-MB levels during the study observation period were significantly lower in L-carnitine treated patients than in control group.
- L-carnitine was also associated with a lower total release time and a lower rate of CPK-MB release as compared with values seen in control patients, although differences between the two groups did not reach statistical significance.

KEY POINT

- **The effects of L-carnitine on levels of the prognostic indicator, CPK-MB, suggest that L-carnitine may limit the extent of necrotic damage in the myocardium following AMI**

Myocardial carnitine deficiency in acute myocardial infarction

Spagnoli LG, Corsi M, Villaschi S et al.

Lancet 1982;1(8286):1419-20

BACKGROUND AND AIM

- Findings strongly suggest that the maintenance of physiological levels of carnitine and the acylcarnitine to free carnitine ratio play an important role in the control of the metabolism of the injured myocardium.
- This study compared heart carnitine levels at autopsy in patients who had died from acute myocardial infarction or from causes other than heart disease (controls).

MATERIALS AND METHODS

- In the first group (n=7) the tissue samples were removed from the necrotic area, from the border zone, and from the healthy myocardium, whereas in the controls (n=4) samples were collected from the left ventricular walls.

RESULTS

- Low carnitine concentrations have been found in necrotic areas of myocardium of patients who had an AMI, whereas carnitine levels were normal in surrounding healthy myocardial tissue; carnitine concentrations were also intermediate in the border zone between necrotic and healthy tissue.
- There were no differences between the carnitine concentrations found in the healthy tissue of AMI patients versus controls.
- Neither short- nor long-chain carnitine esters were found in the tissue fragments of either group, presumably because in specimens removed 24 hours after death, all the carnitine content is present in the free isomer form.

KEY POINT

- **The results of this study confirm carnitine depletion in necrotic areas of myocardium and also suggest that the intermediate carnitine values, found in the infarct border zones between necrotic and healthy tissue, reflect an area of reversible metabolic injury for which restoration of adequate carnitine levels might be beneficial**

L-carnitine as an adjunct therapy to percutaneous coronary intervention for non-ST elevation myocardial infarction

Xue YZ, Wang LX, Liu HZ et al.

Cardiovasc Drugs Ther 2007;21(6):445-8

BACKGROUND AND AIM

- The elevation in myocardial markers such as creatine kinase-MB (CK-MB) and troponin-I has a strong positive relationship with the adverse clinical outcomes after percutaneous coronary intervention (PCI). In several clinical trials, treatment with L-carnitine significantly decreased the levels of CK-MB and troponin-I (markers of cardiac injury).
- This study evaluate the effects of L-carnitine as an adjunct therapy to PCI for non-ST elevation acute coronary syndrome (NSTEMI).

MATERIALS AND METHODS

- Patients (n=96) with NSTEMI underwent PCI and were randomly assigned to receive, in double-blind fashion, L-carnitine (n=48) or placebo (n=48). All patients also underwent PCI within 24 hours from the onset of chest pain. The dosage of L-carnitine was 5 g intravenously as a bolus 30 minutes before PCI, followed by 10 g per day intravenously for the next three days. The peak values of CK-MB and troponin-I before and after PCI were observed.

RESULTS

- Before PCI there was no significant difference in CK-MB and troponin-I, while mean peak values for CK-MB at 12 and 24 hours after PCI were significantly lower in the L-carnitine group than in the placebo group (*Figure A*).
- The mean peak value for troponin-I at 8 hours was also significantly lower in the L-carnitine group than in the placebo group (*Figure B*).

KEY POINT

- **The addition of L-carnitine before and immediately following PCI reduces the post-PCI levels of CK-MB and troponin-I, indicating diminished myocardial injuries**

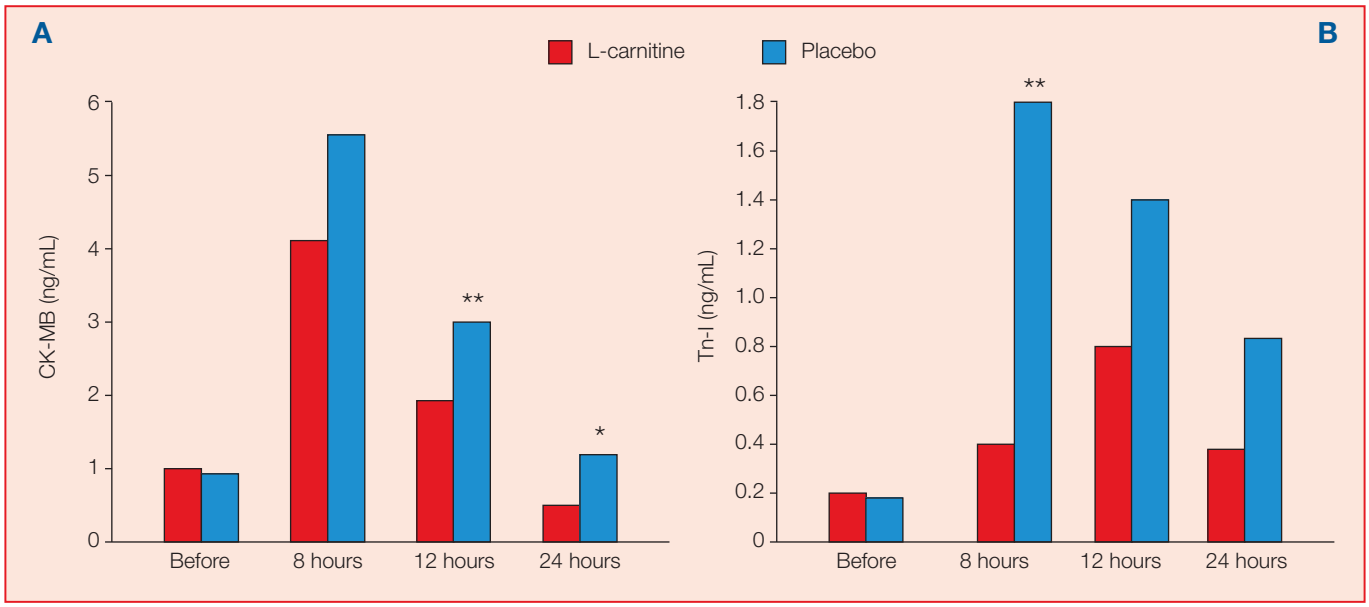


Figure. Mean peak value for **A** creatine kinase-MB (CK-MB) and **B** troponin-I (Tn-I) in the placebo and L-carnitine groups (*p<0.05; **p<0.01).

Controlled study on L-carnitine therapeutic efficacy in post-infarction

Davini P, Bigalli A, Lamanna F, Boem A.

Drugs Exp Clin Res 1992;18(8):355-65

BACKGROUND AND AIM

- Carnitine plays a role in myocardial energy production by facilitating the transport of fatty acids into mitochondria. Myocardial carnitine depletion occurs during ischemia, and carnitine deficiency might exacerbate ischemia and contribute to the pathogenesis of acute myocardial infarction (AMI).
- This study aimed to determine if chronic treatment with L-carnitine modified the incidence of complications and deaths over a 12-month period following hospital discharge in patients surviving an AMI.

MATERIALS AND METHODS

- The study was performed in a cohort of 160 patients discharged from hospitalization following the diagnosis of a recent AMI. The study design was open, with a control group, with treatment randomly assigned. Group A (n=81) was treated with oral L-carnitine administered at the dose of 4 g/day for 12 months; group B (n=79) served as control group. Patients in both the control and treatment groups were also maintained on appropriate pharmacological treatment.

RESULTS

- After 12 months, patients treated with L-carnitine showed, in comparison with controls, a significant improvement in heart rate ($p<0.005$) and systolic arterial pressure ($p<0.005$), a decrease of angina attacks ($p<0.005$) and a clear improvement in the lipid pattern ($p<0.005$).
- This changes were also accompanied by lower mortality in the L-carnitine group (1.2% vs 12.5% in the control group, $p<0.005$) [*Figure*].

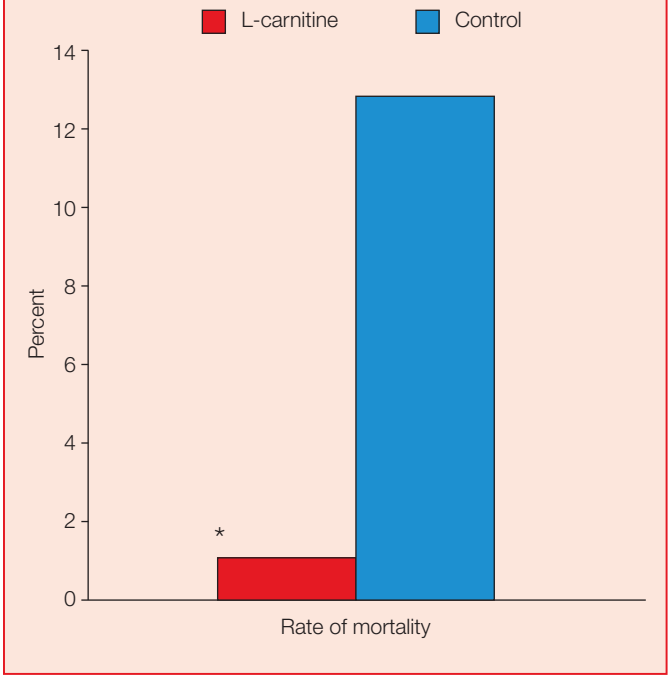


Figure. Rate of mortality in post-heart attack subjects following treatment with L-carnitine (*$p<0.005$).

KEY POINT

- **In patients diagnosed as having a recent AMI, a dose of 4 g/day L-carnitine over 12 months, in addition to the pharmacological treatment generally used, improved quality of life with decreased incidence of arrhythmias and angina and, most importantly, increased life expectancy with a remarkable and significant reduction in mortality**

Effect of L-carnitine on the limitation of infarct size in one-month post-myocardial infarction cases. A multicentre, randomised, parallel, placebo-controlled trial

Jacoba KGC, Abarquez RF, Topacio GO et al.

Clin Drug Investig 1996;11(2):90-6

BACKGROUND AND AIM

- It's well known that myocardial carnitine depletion occurs during ischemia. The protective activity of L-carnitine has been shown in experimental models of acute heart ischemia, in addition, several clinical studies in myocardial infarction reported a favourable effect of the compound on size of necrotic area and on ventricular arrhythmias.
- This multicenter, double-blind, randomized parallel, placebo-controlled study evaluated the capability of L-carnitine to reduce the extent of necrotic area in patients with a confirmed diagnosis of acute myocardial infarction (AMI).

MATERIALS AND METHODS

- A total of 39 patients who met the inclusion criteria (confirmed diagnosis of AMI based on clinical history, serial ECG changes and enzyme elevations) were randomized to receive placebo (n=17) or L-carnitine (n=22) 2.97 g/day in addition to all other current medications, for 2 months. One month after AMI, patients in both groups underwent technetium-99m (Tc99m) SPECT (Single Photon Emission Tomography) rest stress study which was repeated after 2 months of treatment.

RESULTS

- Within-group analysis showed that the increase in the sum of the pre- and post-treatment resting scores was highest in the area of the left anterior descending artery (70, $p<0.032$) followed by the right coronary artery segment (45, $p<0.018$) in the L-carnitine group. This increase indicates myocardial viability; there was no significant increase in the sum of the resting score in the region of the left circumflex artery during the resting study in the L-carnitine group (*Figure*).

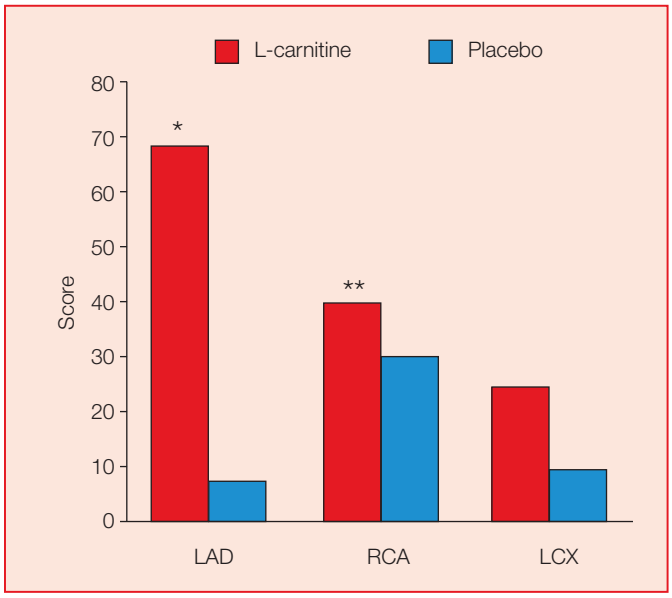


Figure. Resting score (Wilcoxon's signed rank test) after treatment using technetium-99m Hexa-MIBI SPECT (*$p<0.032$; **$p<0.018$). LAD=left anterior descending artery; LCX=left circumflex artery; RCA=right coronary artery.

KEY POINTS

- Two months' treatment with L-carnitine can significantly increase heart muscle viability when taken 1 month following AMI
- L-carnitine gives greater improvement in myocardial viability in the areas of the left anterior descending and right coronary artery distributions