L-carnitine for the Treatment of Acute Myocardial Infarction

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Although the therapeutic strategies available for treating acute myocardial infarction (AMI) have evolved dramatically in recent decades, coronary artery disease remains the leading cause of death in our society, and the rates of recurrent myocardial infarction and mortality are still unacceptably high. Therefore, exploration of alternative therapeutic strategies for AMI is of utmost importance. One such strategy is to target metabolic pathways via L-carnitine supplementation. L-carnitine is a physiologically essential metabolic cofactor that has been shown to provide a plethora of benefits when administered after AMI. L-carnitine has been shown to lessen infarct size, to reduce ventricular arrhythmias, left ventricular dilation, and heart failure incidence, as well as improve survival. These benefits may, in part, be related to its ability to boost glucose oxidation in ischemic tissues, while moderating increases in fatty acyl-coenzyme A levels that can impair mitochondrial efficiency and promote oxidative stress and inflammation. This article summarizes the evidence pertinent to the therapeutic use of L-carnitine for AMI.

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Acute myocardial infarction (AMI) is very common in the United States, with a prevalence of 3.1% in the US adult population > 20 years of age.[1] It is estimated that there are 610,000 new and 325,000 recurrent AMIs each year.[1] Approximately every 34 seconds another person has an AMI in the United States, and approximately 15% of patients who have an AMI will die as a direct result.[1] After an AMI, 22% of patients aged > 65 years will have a recurrent AMI, whereas 15% of men and 22% of women aged < 65 years will have a recurrent AMI.[1] The average survival duration is 17 years after an AMI in men and 13.3 years in women between the ages of 55 and 64 years, 9.3 years and 8.8 years

for men and women between the ages of 65 and 74 years, and only 3.2 years for patients > 75 years.[1] Coronary heart disease (CHD) is responsible for one of every six deaths in the United States[1]; additionally, CHD is a source of significant cost to the health care system. In the United States, CHD costs $108.9 billion annually.[2] There is an urgent need for development of more effective strategies to prevent and treat AMI. The nutrient carnitine shows intriguing promise in this regard.

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Physiologic Role of Carnitine

Carnitine is a physiologically essential quaternary amine synthesized in the liver and kidneys, and is found in meat and dairy products, but not plant-based foods. Carnitine's best-known physiologic function is to enable the transport of long-chain fatty acids into mitochondria. Long-chain fatty acyl-coenzyme A (fatty acyl-CoA) cannot directly enter the mitochondrial inner matrix for oxidation; rather, it must first be converted to fatty acyl-carnitine by the enzyme carnitine palmitoyltransferase-1, located in the mitochondrial outer membrane.[3] Fatty acyl-carnitine can then be translocated to the inner matrix by the transport protein acylcarnitine-carnitine translocase. Carnitine palmitoyltransferase-2, on the inner side of the inner mitochondrial membrane, then resyn-thesizes fatty acyl-CoA from the transported fatty acyl-carnitine; this fatty acyl-CoA can now be oxidized within the mitochondrion, and the liberated carnitine can be shuttled back to the cytoplasm. Carnitine is also a substrate for the enzyme carnitine acetyltransferase, found in the mitochondrial inner matrix, the cytoplasm, and the nucleus. When acetyl-coenzyme A (acetyl-CoA) accumulates in mitochondria, this enzyme converts it to acetylcarnitine; this compound can be transported to the cytoplasm or nucleus, where the same enzyme can regenerate acetyl-CoA for use in lipid biosynthesis or acetylation reactions.[4,5] Hence, L-carnitine can best be viewed as a buffer and transporter for long-chain fatty acyl as well as acetyl groups.

Carnitine Promotes Glucose Oxidation in Ischemic Tissue

Although carnitine is typically viewed as a catalyst for fatty acid oxidation (and low myocardial carnitine levels in certain pathologies can compromise the efficiency of myocardial fatty acid oxidation[3]), it also has the potential to promote myocardial oxidation of glucose. Particularly within the context of myocardial ischemia or fatty acid oversupply, carnitine administration has been shown to increase the relative proportion of energy provided by mitochondrial pyruvate oxidation.[6,7] This reflects the fact that the mitochondrial acetyl-CoA to CoA ratio increases during ischemia, as Krebs cycle activity slows; in turn, this results in allosteric activation of pyruvate dehydrogenase kinase, which phosphorylates (and thereby diminishes the activity of) its target pyruvate dehydrogenase. Hence, glycolytically derived pyruvate—or lactate extracted from the blood—becomes less available for oxidation in the Krebs cycle. Carnitine administration, compensating for a reduction in the free carnitine pool, tends to reverse this effect by boosting conversion of acetyl-CoA to acetylcarnitine, lowering the acetyl-CoA to CoA ratio and thereby diminishing the activity of pyruvate dehydrogenase kinase.

This is beneficial for at least two reasons: (1) mitochondrial generation of adenosine triphosphate (ATP) from pyruvate is more "O_2 efficient" than generation of ATP from fatty acids; and (2) oxidation of fatty acids provides approximately 6% less ATP per unit O_2 consumed as compared with pyruvate oxidation.[8] When O_2 availability is limited because of ischemia, this can be beneficial. Carnitine may also improve bioenergetic efficiency during myocardial ischemia by increasing the availability of free coenzyme A for α-ketoglutarate dehydrogenase.

Perhaps more importantly, oxidation of pyruvate lessens myocardial production of lactate, decreasing the acid load on the heart. A decrease in myocardial intracellular pH causes Na^+ accumulation, via the Na^+/H^+ exchanger, which in turn reverses Ca^{+2} transport through the Na^+/Ca^{+2} exchanger, leading to intracellular Ca^{+2} overload that compromises contractile efficiency.[9] Thus, improved efficiency of pyruvate oxidation is energetically beneficial to the ischemic myocardium while preventing myocardial acidosis and its adverse impact on contractile function. In this regard, direct inhibition

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of pyruvate dehydrogenase kinase with dichloroacetate, or genetic knockout of this enzyme, is protective in mouse models of cardiac ischemia-reperfusion.[10]

Benefits of Buffering Fatty Acyl-CoAs

Increased myocardial carnitine levels also act as a buffer for fatty acyl-CoA levels, both in myocardiocytes and in cardiac vascular endothelium; in other words, fatty acyl-CoA levels tend to decline after carnitine administration owing to increased synthesis of fatty acyl-carnitine. This may lessen the production of certain proinflammatory, prooxidative lipid metabolites, such as ceramide and diacylglycerol, which can mediate cardiac lipotoxicity as well as endothelial dysfunction.[11] In rodent models of heart failure (HF), these lipid mediators have been shown to promote cardiac hypertrophy, contractile dysfunction, and cardiomyocyte apoptosis. It has also been suggested that elevated levels of fatty acyl-CoA can disrupt myocardial membrane structure during acute ischemia, promoting oxidative damage to mitochondrial membranes and inducing ischemic ventricular arrhythmias (VA).[12,13] This may reflect the fact that fatty acyl-CoAs can inhibit the mitochondrial adenine nucleotide translocator (ANT), which moves newly synthesized ATP to the cytoplasm while concurrently bringing adenosine diphosphate into the mitochondrial matrix[14-16]; inefficient ANT activity impairs cellular bioenergetics while boosting mitochondrial superoxide production. The buffering activity of carnitine presumably would be protective in these respects.[17]

Potential Utility of Carnitine Administration in AMI

In aggregate, these considerations suggest that L-carnitine administration could favorably influence the bioenergetics and the structural and functional integrity of the ischemic and postischemic heart. In fact, the controlled clinical studies (summarized below), as well as preclinical studies in animals, indicate that carnitine administration subsequent to a myocardial infarction may have the potential to reduce risk for VA and sudden cardiac death; decrease the extent of cardiac necrosis, postinfarct cardiac remodeling, and ventricular dilatation (phenomena that predispose to cardiac failure and death); lessen the damage to the microvasculature ("no-reflow" phenomenon) that often impedes restoration of appropriate cardiac blood flow following thrombolytic therapy[18]; and improve survival.

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Accumulation of acyl-CoA compounds has been postulated as a cause of VA, which is one of the most common causes of death in patients with a history of AMI. Indeed, it has long been suspected that exposure to excessive free fatty acids and their metabolites during an AMI is a key cause of sudden death.[19] This accumulation comes about not only because of a decline in mitochondrial respiration stemming from myocardial hypoxia, but also because the systemic stress response liberates free fatty acids from adipose stores; the venerable glucose-insulin-potassium strategy for treatment of AMI was intended to block this excessive flux of free fatty acids.[20,21] By decreasing fatty acyl-CoA levels, carnitine administration could be predicted to decrease the risk for VA and sudden cardiac death during AMI, as has been observed clinically.

L-carnitine has also been shown to decrease left ventricular (LV) dilatation after an AMI[22]; LV dilatation, an important prognostic factor for clinically relevant events,[23] initially occurs by thinning and expansion of the infarcted area, and later is followed by a compensatory lengthening of the noninfarcted myocardial regions, all of which help to maintain a more normal stroke volume.[23] The lengthening of the normal myocardial area reflects LV remodeling. Despite its being a compensatory response, patients with a dilated LV are prone to developing cardiac failure, VA, and death. Preventing the remodeling process would effectively reduce LV dilatation. L-carnitine therapy of AMI has the potential to prevent LV dilatation, both by mitigating the extent of myocardial necrosis via its favorable impact on the bioenergetics of acutely hypoxic myocardial tissue, and by opposing the process of ventricular remodeling. It is pertinent that rodents genetically prone to over-accumulation of fatty acids and their metabolites (such as those heterozygous for carnitine palmitoyltransferase-1 deficiency) are more prone to develop severe cardiac hypertrophy and cardiomyopathy during pressure overload.[9,24] Ceramide and diacylglycerol appear to play a role in mediating this process.[9] Because L-carnitine can effectively

L-carnitine has also been shown to decrease left LV dilatation after an AMI…

TABLE 1

Trials Showing a Reduction in Infarct Size Using L-carnitine in Acute Myocardial Infarction

Study	Intervention	N	Outcome
Rebuzzi AG et al[30]	L-carnitine, 40 mg/kg/d × 5 d	22	CPK-MB significantly lower in L-carnitine group as compared with control (*P* value not stated)
Jacoba KGC et al[29]	L-carnitine 3 g/d	39	Necrotic area as determined by ^{99m}Tc-Hexamibi SPECT reduced in L-carnitine group
Singh RB et al[28]	L-carnitine 2 g/d × 28 d	101	CK: size of necrosis (g equivalents) significantly less in the L-carnitine group (95.5 [23.6])[a] vs placebo (116.2 [26.2]), enzyme peak (IU/L) (1.48 [0.78])[b] vs (1.88 [0.92]), and AUC (3275 [955])[a] vs (4307 [1150]), respectively; CK-MB: size of necrosis (g equivalents) significantly less with L-carnitine group (58.6 [16.6])[a] vs placebo (73.3 [21.5]) and enzyme peak (IU/L) (1.32[0.4])[b] vs placebo (1.55 [0.6]), respectively; QRS score lower in L-carnitine group (7.4 ± 1.2[a] vs 10.7 ± 2.0); Serum AST and lipid peroxides lower and LDH higher in L-carnitine group; lower incidence of angina (17.6 vs 36.0%), NYHA class III and IV HF plus LV enlargement (23.4% vs 36.0%), total arrhythmias (13.7% vs 28.0%) and total cardiac events (15.6% vs 26.0%) in L-carnitine group
Xue Y et al[37]	L-carnitine 5 g IV bolus followed by 10 g/d IV infusion × 3 d	96	CK-MB at 12 and 24 h after PCI were less in L-carnitine group ($P < .01$); troponin-I was lower in the L-carnitine group at 8 h after PCI ($P < .01$)

[a] $P < .01$, comparing carnitine and placebo groups.
[b] $P < .05$.
^{99m}Tc-Hexamibi SPECT, technetium-99m-Hexakis (methoxyisobutylisonitrile) technetium [i] single-photon emission computed tomography; AST, aspartate transaminase; AUC, area under the curve; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; CPK-MB, creatinine phosphokinase-myocardial band; HF, heart failure; IV, intravenous; LDH, lactate dehydrogenase; LV, left ventricular; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

attenuate the increase in LV size in patients with a history of AMI, it seems likely that treatment with L-carnitine will be associated with a more favorable prognosis (Tables 1-3).[25-37]

Trials Testing L-carnitine in AMI

Rebuzzi AG et al. Drugs Exp Clin Res. *1984;10:219-223*

The necrotic area after an AMI is a prognostic indicator for the development of complications and death.[30] The first study to evaluate the effect of L-carnitine in AMI tested its ability to reduce creatinine phosphokinase-myocardial band (CPK-MB), an indicator of the extent of necrotic area. A total of 22 patients were enrolled, 12 of whom were treated with L-carnitine (40 mg/kg/d); the remaining patients were treated with standard therapy without L-carnitine. Dosage form, blinding, and randomization were not mentioned. Patients receiving L-carnitine were divided into two groups: those in whom treatment was started within 4 hours of the onset of symptoms and those in whom treatment was started after > 4 hours from symptom onset. The serum CPK-MB enzyme was quantified in both the groups. The CPK-MB release, as well as the maximum level of CPK-MB in the group treated with L-carnitine, was significantly lower than that of the control group (statistical significance indicated but *P* values not provided). There was a tendency for improvement in patients who were treated earlier. Although the sample size of this study was too small to make any firm conclusions, treatment with L-carnitine may provide benefit after an AMI by promoting a lower serum level of CPK-MB when compared with lack of L-carnitine treatment. Because CPK-MB is a measure of the size of necrotic tissue, it can

TABLE 2

Thirteen Clinical Trials Testing L-carnitine in Acute Myocardial Infarction

Study	N	Intervention	Results
Rebuzzi AG et al[30]	22	L-carnitine 40 mg/kg/d × 5 d (dosage form not stated)	CPK-MB lower in L-carnitine group as compared with control
Rizzon P et al[27]	56	L-carnitine 100 mg/kg IV every 12 h × 36 h for 4 doses	Lower incidence of premature ventricular beats ($P < .05$) and ventricular tachycardias ($P < .05$) in the L-carnitine group
De Pasquale B et al[31]	146	L-carnitine: 3 g every 8 h slow IV infusion for the first 3 days, 2 g orally every 8 h on d 4-7, and 2 g orally every 12 h on d 8	18 deaths (18.6%) in the placebo group, no deaths in the L-carnitine group
Davini P et al[32]	160	L-carnitine 4 g/d (2 g BID) orally for 1 y	Improved heart rate ($P < .005$), systolic BP ($P < .005$), diastolic BP ($P =$ not significant) and lipid pattern ($P < .005$); lower incidence of anginal attacks ($P < 005$), rhythm disorders ($P =$ not significant) and clinical features of dysfunction of myocardial contractility ($P =$ not significant) in L-carnitine group; lower mortality rate in L-carnitine group (1.2% vs 12.5%; $P < .005$)
Martina B et al[33]	20	L-carnitine 5 g of L-carnitine at 0, 12, 24, & 36, h; then 6 g (2 × 3 g) d 3-7 via IV infusion	No difference in incidence of premature ventricular beats; on d 2 after AMI; significantly lower incidence of high-grade premature ventricular beats in L-carnitine group ($P = .028$)
Iliceto S et al[22]	472	L-carnitine 9 g/d (continuous IV infusion) × first 5 days, then 6 g/day PO (2 g TID) × 12 mo	Reduced LV dilatation in L-carnitine group; less % increase in the end-diastolic and end-systolic volumes in L-carnitine group
Jacoba KGC et al[29]	39	L-carnitine 2.97 g/day PO	Necrotic area as determined by ^{99m}Tc-Hexamibi SPECT less in L-carnitine group
Pehlivanoglu S et al[34]	18	L-carnitine 9 g/d IV × 5 d then 3 g/d PO × 3 mo	No statistically significant difference between the groups in wall motion indices or ejection fraction
Singh RB et al[28]	101	L-carnitine 1.98 g/d × 28 d	QRS score lower in L-carnitine group (7.4 ± 1.2 vs 10.7 ± 2.0); serum AST and lipid peroxides lower and LDH higher in L-carnitine group; lower incidence of angina (17.6 vs 36.0%), NYHA class III and IV HF plus LV enlargement (23.4 vs 36.0%), total arrhythmias (13.7 vs 28.0%) and total cardiac events (15.6 vs 26.0%) in L-carnitine group
Iyer R et al[26]	60	L-carnitine 6 g/d IV for 7 d, then 3 g/d PO (1 g TID) for 3 mo	No significant difference in the echocardiographic parameters, EF, end-systolic volume, or end-diastolic volume

(*Continued*)

Thirteen Clinical Trials Testing L-carnitine in Acute Myocardial Infarction (*continued*)

Study	N	Intervention	Results
Kobulia B et al[35]	98	L-carnitine 9 g/d (3 g TID IV) for 5 d, then 4 g/d (2 g× 2) orally from 6th to 180th d	Lower incidence of death (9.7% vs 12.3% at 6 mo; $P < .05$), reinfarctions, and heart, and the combined endpoint of death or reinfarction by 15.7% in L-carnitine group
Tarantini G et al[36]	2330	L-carnitine 9 g/d continuous IV infusion first 5 d, then 4 g/d PO × 6 mo	No difference in the incidence of the primary endpoint at 6 mo; 5-d mortality was lower in the L-carnitine group (HR = 0.61, 95% CI, 0.37-0.98, $P = .041$)
Xue Y et al[37]	96	L-carnitine 5 g IV bolus followed by 10 g/d IV infusion × 3 d	CPK-MB at 12 and 24 h after the PCI were less in L-carnitine group ($P < .01$); troponin-I was lower in the L-carnitine group at 8 h after PCI ($P < .01$)

^{99m}Tc-Hexamibi SPECT, technetium-99m-Hexakis (methoxyisobutylisonitrile) technetium [i] single-photon emission computed tomography; AMI, acute myocardial infarction; AST, aspartate transaminase; BID, twice daily; BP, blood pressure; CI, confidence interval; CPK-MB, creatinine phosphokinase-myocardial band; EF, ejection fraction; HF, heart failure; HR, hazard ratio; IV, intravenous; LDH, lactate dehydrogenase; LV, left ventricular; NYHA, New York Heart Association; PO, oral; PCI, percutaneous coronary intervention; TID, three times daily.

TABLE 3

Benefits of L-carnitine Administration in Patients With Acute Myocardial Infarction

Reduced risk for ventricular arrhythmias[a]
Decreased necrosis and infarct size[b]
Decreased oxidative stress[c]
Decreased ventricular remodeling[d]
Reduced risk for angina[e]
Decreased risk for vascular events[f]
Decreased mortality[g]
*Confirmed by meta-analysis[h]

[a]Data from Rizzon P et al,[27] Singh RB et al,[28] Martina B et al.[33]
[b]Data from Rizzon P et al,[27] Singh RB et al,[28] Jacoba KGC et al.[29]
[c]Data from Singh RB et al.[28]
[d]Data from Iliceto S et al,[22] Singh RB et al.[28]
[e]Data from Singh RB et al,[28] Davini P et al.[32]
[f]Data from Singh RB et al,[28] Kobulia B et al.[35]
[g]Data from Singh RB et al,[28] De Pasquale B et al,[31] Davini P et al,[32] Kobulia B et al.[35]
[h]Data from DiNicolantonio JJ et al.[25]

be assumed that the area of necrosis is also significantly decreased with L-carnitine therapy, which may lead to a reduction in complications and lower risk of death in these patients.

Rizzon P et al. Eur Heart J. *1989;10:502-508*

In a double-blind, randomized controlled trial (RCT) conducted on 56 patients with AMI, patients were randomized within 3 to 12 hours from onset of pain to receive either intravenous (IV) L-carnitine, 100 mg/kg IV every 12 hours for 36 hours for 4 doses, or placebo.[27] Free carnitine and acylcarnitine compounds were measured in the serum and urine of the patients in both groups. Additionally, the patients' electrocardiographic recordings for the first 48 hours after admission to the cardiac care unit were monitored for VA. The researchers found that the pretreatment levels of serum free carnitine, short-chain acylcarnitine esters, and long-chain acylcarnitine esters were similar between both groups; however, treatment with L-carnitine significantly increased the quantity of these compounds in the serum ($P < .001$) and the urine ($P < .001$). There was a lower incidence of premature ventricular beats ($P < .05$) and ventricular tachycardias ($P < .05$) in the group receiving L-carnitine as compared with the group receiving placebo. This study supports an antiarrhythmic effect of high-dose IV L-carnitine administration in patients who have had an AMI.

De Pasquale B et al. Cardiologia. *1990;35:591-596*

In a nonrandomized study of 146 patients who had an AMI, patients were assigned to receive either L-carnitine (n = 49) or placebo (n = 97).[31] L-carnitine was given as 3 g every 8 hours as a slow IV infusion for the first 3 days, and

then orally as 2 g every 8 hours from the fourth day to the seventh day, and finally given orally as 2 g every 12 hours on the eighth day. The patients were followed for the first 28 days after hospitalization. There were 18 deaths (18.6%) in the placebo group, whereas there were no deaths reported in the group receiving L-carnitine. Thus, there seems to be a dramatic reduction in the mortality rate in the first 28 days in patients with AMI between those receiving L-carnitine versus those who did not. The results of this study favor the early use of L-carnitine in cases of AMI. However, the clinical characteristics of the patients were not entirely similar between the two groups before the start of the study. Thus, the results of this study should be interpreted with caution.

Davini P et al. Drugs Exp Clin Res. *1992;18:355-365*

A randomized study evaluated the long-term effects of L-carnitine administration in 160 patients with a history of recent AMI.[32] The patients were randomized on discharge from hospital to receive either L-carnitine at a dose of 4 g/d (2 g every 12 h) orally for 12 months in addition to standard medical treatment, or the standard medical treatment alone. The patients receiving L-carnitine, in comparison with the control subjects, showed beneficial effects on heart rate ($P < .005$), systolic arterial pressure ($P < .005$), diastolic arterial pressure ($P =$ not significant), and lipid pattern ($P < .005$). There was a lower incidence of anginal attacks ($P < .005$), rhythm disorders ($P =$ not significant), and clinical features of dysfunction of myocardial contractility ($P =$ not significant) in patients receiving L-carnitine. The mortality rate in the L-carnitine group was significantly lower as compared with the control group (1.2% vs 12.5%; $P < .005$). The results of this study show a definite improvement in both the quality and quantity of life in patients being given L-carnitine for 12 months after an AMI.

Martina B et al. Schweiz Med Wochenschr. *1992;122:1352-1355*

The antiarrhythmic effect of L-carnitine was investigated in a randomized, double-blind study enrolling 20 patients with a history of recent AMI (within 4-12 h after onset of pain).[33] The patients received either 5 g of L-carnitine or placebo at 0, 12, 24, and 36 hours via IV infusion. Additionally, the patients received their allotted treatment again in doses of 2 × 3 g on days 3 through 7 via IV infusion over a time span of 2 hours. The patients were monitored with 24-hour electrocardiogram on days 1, 2, and 7. There was no overall significant difference in the incidence of premature ventricular beats between the groups. However, on the second day after the AMI, there was a significantly lower incidence of high-grade premature ventricular beats in the group receiving L-carnitine as compared with the placebo group (4 of 12 patients receiving L-carnitine versus 7 of 8 patients receiving placebo; $P = .028$). Therefore, there seems to be some efficacy of L-carnitine in preventing high-grade VA in patients receiving L-carnitine after an AMI.

Iliceto S et al. J Am Coll Cardiol. *1995;26:380-387*

The L-carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) trial assessed the efficacy of L-carnitine administration in patients with AMI in preventing LV dilatation.[22] This trial randomized 472 patients with a history of AMI to receive either L-carnitine or placebo started within 24 hours from the start of chest pain. The patients received either placebo or IV L-carnitine at a dose of 9 g/d initially for the first 5 days followed by 6 g/d orally for 12 months. The patients were monitored by echocardiograms conducted at admission and discharge from the hospital, and at 3, 6, and 12 months after the AMI. In the first year after AMI, there was a significant reduction in LV dilatation in the group receiving L-carnitine as compared with the group receiving placebo. The percent increase in the end-diastolic and end-sys-tolic volumes during the follow-up period was significantly less in the group receiving L-carnitine ($P = .02$ and $P = .05$, respectively, at 12 months). There was no statistically significant difference between the groups in terms of LV ejection fraction, the combined endpoint of death and HF, and the incidence of ischemic events. However, there were signals for a reduction in mortality (10 [4.3%] vs 13 [5.4%]) and HF incidence (4 [1.7%] vs 10 [4.2%]), respectively, with L-carnitine at 1-year follow-up when compared with placebo. Thus, L-carnitine may decrease the subsequent sequelae after an AMI; however, further studies are required.

Jacoba KGC et al. Clin Drug Invest. *1996;11:90-96*

The effect of L-carnitine on the extent of infarcted myocardial area in patients with a history of AMI was evaluated in 39 patients.[29] Patients were randomized to receive either 2.97 g (contained within 3 tablets 3 times daily) of L-carnitine per day or placebo and were followed every 2 weeks for 8 weeks. The researchers used technetium-99m-Hexamibi (Hexakis [methoxyisobutylisonitrile] technetium [i]) single-photon emission

computed tomography (SPECT) to determine the necrotic area of the myocardium in all patients. In the L-carnitine group, the sum of pretreatment and posttreatment resting scores, indicating myocardial viability, was the highest in the myocardial area supplied by the left anterior descending artery ($P < .032$) followed by the area supplied by the right anterior descending artery ($P < .018$), indicating an increase in myocardial viability. In contrast, there was no significant increase in the pretreatment and posttreatment resting scores in the group receiving placebo. During the stress test, there was no increase in the nonparametric scores in the posttreatment period in either of the groups in the areas supplied by any of the arteries. Moreover, there were no differences between the intervention and placebo groups. The authors attributed the lack of statistically significant differences between the two groups to the small sample size of this study. Nevertheless, this study shows that L-carnitine administration after AMI improves myocardial viability.

Pehlivanoglu S et al. Türk Kardiyol Dern Arş-Arch Turk Soc Cardiol. *1996;24:251-255*

A study conducted on patients with a first AMI treated with thrombolytic agents enrolled 30 patients within 6 hours of diagnosis of an AMI.[34] The patients were treated with either IV L-carnitine, 9 g/d, for the first 5 days followed by 3 g/d orally for 3 months, or placebo. Patients were then monitored by echocardiograms and radionuclide ventriculography. The wall motion indices in both groups improved significantly over the study duration; however, there was no statistically significant difference between the groups (36% increase in intervention group vs 31% increase in the placebo group). Additionally, there was no statistically significant difference within any group or between the groups in terms of LV diastolic volume indices. Three months after the start of the study, there was a numerically larger increase of 31% in the ejection fractions of those in the L-carnitine group and a 24% increase in those in the placebo group. Although this represented a significant increase in both groups, differences between groups were not statistically significant. The results of this study, therefore, showed no benefit of L-carnitine administration on wall motion index, LV diastolic volume index, or ejection fraction in patients with AMI who received thrombolytic agents.

Singh RB et al. Postgrad Med J. *1996;72:45-50*

This randomized, double-blind placebo-controlled trial enrolled 101 patients with a history of AMI (within 24 hours of symptom onset) to receive either 1.98 g/d of oral L-carnitine for 28 days or placebo.[28] There was a significantly greater reduction in cardiac enzymes at the end of the treatment period in the L-carnitine group as compared with the placebo group. Estimation of the size of infarcted area was done by the QRS score based on the electrocardiographic assessment of patients. Creatine kinase was significantly less in the L-carnitine group versus the placebo group; size of necrosis (g equivalents) (95.5 [23.6]) versus (116.2 [26.2]; $P < .01$), enzyme peak (IU/L) (1.48 [0.78]) versus (1.88 [0.92]; $P < .05$), and area under the curve (3275 [955]) versus (4307 [1150]; $P < .01$), respectively. CPK-MB was also significantly reduced with L-carnitine versus placebo; size of necrosis (g equivalents) (58.6 [16.6]) versus placebo (73.3 [21.5]; $P < .01$), and enzyme peak (IU/L) (1.32[0.4] versus 1.55 [0.6]; $P < .05$), respectively. The QRS score was significantly lower in the interventional group as compared with the placebo group (7.4 ± 1.2 vs 10.7 ± 2.0). The levels of serum aspartate transaminase (AST) and lipid peroxides were also significantly decreased, whereas lactate dehydrogenase (LDH) levels showed a smaller increase in the L-carnitine group as compared with placebo. The L-carnitine group showed a lower incidence of angina pectoris (17.6 vs 36.0%), New York Heart Association class III and IV HF plus LV enlargement (23.4 vs 36.0%), total arrhythmias (13.7 vs 28.0%), and total cardiac events (15.6 vs 26.0%) as compared with placebo. This study showed short-term beneficial effects of L-carnitine administration in patients with AMI. Despite this fact, there have been concerns about the integrity of this trial.

Iyer R et al. J Postgrad Med. *1999;45:38-41*

This RCT enrolled 60 patients with AMI and randomly assigned them to receive either IV L-carnitine at a dose of 6 g/d initially for 7 days followed by 3 g/d orally for 3 months, or placebo.[26] Patients were followed with echocardiograms and 44 patients completed the study duration. One patient died in the group receiving L-carnitine and 3 patients in the placebo group died ($P > .05$). There was no significant difference in the echocardiographic parameters ($P > .05$), LV ejection fraction, end-systolic volume, or end-diastolic volume ($P > .05$). There were no adverse effects in either group. The results of this study could not support a significant beneficial role of L-carnitine administration in patients with AMI on echocardiographic parameters or hard endpoints, as event rates were low and the trial was not powered to test these hard outcomes.

Kobulia B et al. Ann Biomed Res Educ. *2002;2:240-242*

L-carnitine treatment was given in addition to standard medical therapy compared with standard medical therapy alone in patients with AMI < 12 hours between symptoms and randomization.[35] The study enrolled 98 patients with ST-elevation MI (STEMI) and randomized them to either IV L-carnitine, 9 g/d for 5 days followed by 4 g/d orally for 6 months, or the control group. The primary outcome of the trial was the combined occurrence of death and HF at 6 months after the start of treatment. There was a significantly lower incidence of death in the group treated with L-carnitine as compared with the control group (9.7% vs 12.3% at 6 months; $P < .05$). Similarly, there were fewer cases of reinfarctions and HF in the L-carnitine group. L-carnitine reduced the incidence of reinfarction and the combined endpoint of death or reinfarction by 15.7%. L-carnitine therapy after AMI, therefore, significantly reduced the mortality, reinfarction, and HF rate.

Tarantini G et al. Cardiology. *2006;106:215-223*

The efficacy of L-carnitine in reducing the mortality and risk of HF in cases of AMI was evaluated by the CEDIM 2 trial.[36] This was a randomized, double-blind, multicenter trial enrolling 2330 patients with AMI (onset of symptoms within 12 hours of randomization). Patients were randomized to receive either L-carnitine, 9 g/d by continuous IV infusion for the first 5 days followed by 4 g/d orally for the next 6 months, or placebo. The composite primary endpoint of this study was a combination of death and HF at 6 months. The secondary endpoint was the 5-day mortality rate. There was no difference between the two groups in the incidence of the primary endpoint at 6 months (9.2% in L-carnitine group vs 10.5% in the placebo; $P = .27$). However, the secondary endpoint of 5-day mortality was significantly lower in the L-carnitine group as compared with the control group (hazard ratio = 0.61, 95% confidence interval [CI], 0.37-0.98; $P = .041$). There was a 12% lower incidence of mortality in the L-carnitine group at 6 months as compared with placebo; however, this difference was not significant ($P = .48$). The rates of adverse effects were similar with both treatments. This trial showed that L-carnitine supplementation after AMI reduced the incidence of early mortality rate but did not affect the mortality rate or risk of HF at 6 months.

Xue Y et al. Cardiovasc Drugs Ther. *2007;21:445-448*

A total of 96 patients with non-STEMI (NSTEMI) were enrolled to assess whether the addition of L-carnitine in patients undergoing percutaneous intervention (PCI) showed any additional benefit.[37] Patients were randomly assigned to receive either L-carnitine, 5 g/d as an initial IV bolus followed by 10 g/d IV for 3 days, or placebo. The values of CPK-MB at 12 and 24 hours after the PCI were significantly less in the group receiving L-carnitine ($P < .01$). Similarly, the values of troponin-I were significantly lower in the L-carnitine group at 8 hours after PCI ($P < .01$). L-carnitine therapy was independently associated with lower CPK-MB ($r = 0.596$; $P < .001$) and troponin-I ($r = 0.633$; $P < .001$) levels. Cardiac biomarkers are representative of myocardial damage; therefore, the results of this study suggest that L-carnitine is able to limit the extent of myocardial damage after NSTEMI in patients undergoing PCI.

Meta-analysis of L-carnitine for the Secondary Prevention of Cardiovascular Disease

A meta-analysis was recently conducted to assess whether L-carnitine would lead to any beneficial effects on morbidity or mortality in patients who had an AMI.[25] This review included 13 controlled trials with a total of 3629 patients and compared the effects of L-carnitine with placebo or control on mortality rate and incidences of VA, angina, HF, and reinfarction. L-carnitine was shown to lead to a 27% decrease in all-cause mortality (odds ratio [OR] = 0.73, 95% CI, 0.54-0.99; $P = .05$; relative risk [RR] = 0.78, 95% CI, 0.60-1.00; $P = .05$), a 65% decrease in the incidence of VA (RR 0.35 = 95% CI, 0.21-0.58; $P < .0001$) and a 40% decrease in the incidence of angina (RR 0.60 = 95% CI, 0.50-0.72; $P < .00001$). Conversely, there was no decrease in the incidence of HF (RR = 0.85, 95% CI, 0.67-1.09; $P = .21$) or AMI (RR = 0.78, 95% CI, 0.41-1.48; $P = .45$). However, there was a signal for improvement on both of these outcomes. Moreover, it was reported by Kobulia and colleagues[35] that L-carnitine led to a 43.5% reduction in the incidence of HF and a 15% reduction in the incidence of AMI and death; however, the actual numbers for HF and AMI could not be obtained and thus could not be included in the meta-analysis. Clearly, if these had been included, a possible trend or a level of significance might have been reached for HF and/or AMI outcomes.

From the clinical trials, a minimal effective dose seems to be 2 g/d of L-carnitine, with an optimal dosing of approximately 6 to 9 g/d. It is clear that, moving forward, larger clinical trials are required to test L-carnitine in patients who

have had an AMI. It seems logical that a future trial would use IV dosing for the first 5-days post-MI to increase L-carnitine concentrations as quickly as possible, with subsequent oral dosing for the months to follow.

Safety and Tolerability of L-carnitine

L-carnitine has a long history of being well tolerated, with minimal (if any) side effects reported. There were no major adverse effects reported by any of the clinical trials.[22,23,26-37] In these trials, when L-carnitine was compared with placebo or control, no excess incidence of any serious adverse events was apparent in the patients treated with L-carnitine. However, likely owing to inefficient absorption when administered in high supplemental doses,[38] L-carnitine may lead to increased risk of mild gastrointestinal-related symptoms (eg, diarrhea, upset stomach). This inefficiency of absorption also provides a rationale for parenteral administration of carnitine in the days immediately following an AMI, as practiced in some of the trials just cited.

... when L-carnitine was compared with placebo or control, no excess incidence of any serious adverse events was apparent in the patients treated with L-carnitine.

Conclusions

Myocardial ischemia during an AMI leads to a build-up within mitochondria of acetyl-CoA and fatty acyl-CoAs; this can exert a range of adverse metabolic effects. A rise in the acetyl-CoA:CoA ratio inhibits pyruvate dehydrogenase activity, decreasing oxidation of glucose—the most metabolically efficient fuel when oxygen availability is limited—while causing an increase in intracellular acidity that in turn impairs contractile efficiency by boosting intracellular-free calcium. The concurrent rise in fatty acyl-CoAs can impede mitochondrial oxidative phosphorylation and increase mitochondrial superoxide production via inhibition of ANT; moreover, fatty acyl-CoAs can act as biosynthetic precursors for mediators such as ceramide and diacylglycerol that exert proinflammatory effects in cardiac tissue and promote ventricular remodeling. Carnitine serves to buffer increases in both acetyl-CoA and fatty acyl-CoA levels by promoting synthesis of acetylcarnitine and fatty acyl-carnitine; however, a relative deficiency of free carnitine soon develops in ischemic tissue. Hence, effective administration of carnitine following an AMI or other ischemic event serves to moderate the rise in acetyl- and fatty acyl-CoAs and mitigate the adverse consequences of such a rise.

A number of controlled trials have evaluated the utility of administering L-carnitine for some days or months following an AMI. In many of these studies, IV L-carnitine was administered for the first few days, followed by a prolonged course of oral administration. These studies establish, as confirmed by a recent meta-analysis, that L-carnitine administration following AMI can reduce infarct size, decrease risk for VA, diminish LV dilatation, and improve survival. The meta-analysis also found a nonsignificant reduction in risk for HF and a subsequent AMI. Because L-carnitine is inexpensive, natural, and virtually free of side effects (aside from occasional gastrointestinal upset after high oral doses), its use in the treatment of AMI is rational in light of current evidence, and larger RCTs evaluating its benefits in AMI, as an adjunct to current standard management (in the era of intensive lipid-lowering, antithrombotic treatment and invasive treatments) are needed. ■

Dr. DiNicolantonio works for a company that sells L-carnitine supplements but he does not profit from their sale.

Dr. McCarty is owner and science director of NutriGuard Research, Inc. (Encinitas, CA), which sells an L-carnitine supplement. Dr. O'Keefe is the founder and has major ownership interest in CardioTabs (Kansas City, MO), a company that markets nutraceuticals.

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MAIN POINTS

- Acute myocardial infarction (AMI) is very common in the United States, with a prevalence of 3.1% in the US adult population > 20 years of age. Approximately every 34 seconds another person has an AMI in the United States, and approximately 15% of patients who have an AMI will die as a direct result. There is an urgent need for development of more effective strategies.
- Although carnitine is typically viewed as a catalyst for fatty acid oxidation, it also has the potential to promote myocardial oxidation of glucose.
- Carnitine serves to buffer increases in both acetyl-coenzyme A (CoA) and fatty acyl-CoA levels by promoting synthesis of acetylcarnitine and fatty acyl-carnitine; however, a relative deficiency of free carnitine soon develops in ischemic tissue. Hence, effective administration of carnitine following an AMI or other ischemic event serves to moderate the rise in acetyl- and fatty acyl-CoAs and mitigate the adverse consequences of such a rise.
- Studies indicate that carnitine administration subsequent to an AMI may have the potential to reduce risk for ventricular arrhythmia 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.