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# Metabolic Treatment with *L*-Carnitine in Acute Anterior ST Segment Elevation Myocardial Infarction

## A Randomized Controlled Trial

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**Key Words**
Acute myocardial infarction · Myocardial infarction, treatment · Pharmacology, cardiovascular

**Abstract**
***Background:*** Administration of *L*-carnitine in patients with anterior acute myocardial infarction (AMI) prevents left ventricular remodeling. Current study was aimed to assess the effect of *L*-carnitine administration on mortality and heart failure in patients with anterior AMI. ***Methods:*** CEDIM 2 trial was a randomized, double-blind, multicenter, placebo-controlled trial planned to enroll 4,000 patients with acute anterior AMI. The trial was interrupted after the enrolment of 2,330 patients because of the lower than expected enrolment rate. The primary end point was a composite of death and heart failure at 6 months; 5-day mortality was the secondary end point. ***Results:*** During the 6-month follow-up, the primary endpoint was not significantly different between the *L*-carnitine and placebo group (9.2 vs. 10.5%, p = 0.27). A reduction in mortality was seen in the *L*-carnitine arm on day 5 (secondary end-point) from randomization (HR = 0.61, 95% CI 0.37–0.98, p = 0.041). ***Conclusions:*** In CEDIM 2 trial *L*-carnitine therapy led to a reduction in early mortality (secondary end-point) without affecting the risk of death and heart failure at 6 months in patients with anterior AMI, leading to a non-significant finding with respect to the primary end-point.



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## Introduction

Therapeutic strategies aimed at salvaging ischemic myocardium, limiting infarct size and consequent progressive left ventricular dilatation not only preserve global LV function, but also decrease post-acute myocardial infarction (AMI) mortality and heart failure development. These important results are nowadays achieved by thrombolysis or primary transluminal coronary angioplasty, and by beta-blockade and angiotensin-converting enzyme inhibition [1–4]. However, despite improvements in both recanalization and therapies that reduce left ventricular load, AMI mortality still remains high.

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Therefore, efforts are currently made to pursue additional strategies aimed at further increasing myocardial salvage, decreasing left ventricular deterioration and improving survival.

Metabolic protection of ischemic myocardium may exert a beneficial functional effect limiting the deleterious effects of both ischemia and reperfusion and represents a potential basis for additional clinical benefit in patients suffering from AMI [5–8].

Carnitine is a physiologic compound that is essential in producing energy at mitochondrial level; it reduces ischemia-induced increase in long-fatty acid concentration and limits its deleterious functional effect [9]. It has been demonstrated that both the ischemic and infarcted myocardium carnitine depletion rapidly occurs [10] and that its exogenous administration has the potential for beneficially affecting both mechanical and electrical myocardial properties [11–16]. Furthermore, in a randomized multicenter trial (CEDIM trial) [17] it has been shown that *L*-carnitine administration limits LV remodeling in patients with anterior AMI with a significant reduction in the left ventricular volume increase throughout the first year after the acute event. Because of the beneficial effects of *L*-carnitine administration on both electrical and myocardial properties in AMI, and of its potential in limiting progressive LV remodeling, 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.

## Methods

This was a randomized, double-blind, multicenter, placebo-controlled trial. One hundred fifty-three hospitals participated in the trial. Local Ethical Committees approved the study protocol, and each patient provided informed consent to participate.

*Patients*

To be eligible, patients had to have continuous typical chest pain for at least 30 min unrelieved by s.l. or i.v. nitrates, onset of symptoms of AMI within 12 h before randomization, and persistent ST segment elevation of 0.2 mV or more in two or more contiguous precordial leads. Exclusion criteria on admission included: age >80 years, valvular heart disease, hypertrophic cardiomyopathy, congenital heart disease, clinically severe renal or hepatic disorders, severe comorbidity likely to limit the patient's life expectancy, geographic or other factors making study participation impractical, participation in other concomitant trials, alcoholism, pregnancy or lactation, unwillingness to provide informed consent.

*Study Design*

Patients were randomly assigned to receive *L*-carnitine or placebo when arriving at the Cardiology Unit. *L*-Carnitine was administered in the following manner: 9 g per day, by continuous intravenous infusion, for the 5 initial days, and then 4 g per day orally for the next 6 months. The study treatment was added to the standard therapeutic strategies adopted at each Institution. Randomization lists were generated using permuted blocks of variable length in a random sequence so that treatment was balanced within each center. Clinical center was the only stratification factor. Eligible patients were centrally randomized.

Randomization was carried out over the telephone lines by means of a dedicated computer system working 24 h per day, 7 days per week. The initial assessment included a medical history, general physical and cardiovascular examination and recording details of the qualifying AMI. The clinical follow-up visits took place at 1st, 2nd, 4th, and 6th month after enrolment into the trial.

*End Points and Outcome Events*

The primary end-point of the study was the combined occurrence of death and heart failure at 6 months. The end-point of heart failure was not collected until 4 days after enrolment. Heart failure was defined by the presence of: (1) dyspnea, pulmonary rales, evidence of pulmonary congestion at the chest X-ray, plus one of the following criteria: (2) echocardiographic evidence of LV systolic dysfunction as defined by a LV ejection fraction of $\leq 0.40$ (Simpson's method) or a wall motion index $\leq 1.2$ [18], or (3) the need to initiate treatment with digitalis, diuretics, and/or angiotensin-converting enzyme inhibitors or to increase the dosage of these drugs if already prescribed because of history of heart failure. The end-point of heart failure was adjudicated by a committee of three cardiologists, who were blinded to treatment assignment. A blinded core laboratory confirmed chest X-ray and echocardiographic criteria for the diagnosis of heart failure. Discrepancies were solved by consensus. The effect of treatment with *L*-carnitine on 5-day mortality was the secondary end-point of the study. Vital status was ascertained in all but two patients.

*Sample Size*

It was estimated that 4,000 patients had to be enrolled and followed up for 6 months in order to have at least 90% power to detect a 20% relative reduction, from 20 to 16%, in the frequency of the primary end-point with *L*-carnitine as compared with placebo (alpha = 0.05; two-sided).

*Statistical Analysis*

All the analyses were based on the intention-to-treat principle. The primary analysis was based on the comparison, by means of the univariate log-rank test, of the Kaplan-Meier 6-month estimates of the combined incidence of death from any cause or cardiac failure. Most of the secondary analyses were conducted similarly, with different end points and/or at different times. In a set of secondary analyses, a multivariate Cox regression analysis was used to model the incidence of the combined end point and all-cause mortality as a function of a set of independent variables, with the aim of eliminating possible imbalance between the two arms and assessing the presence of interactions between treatment and any of the prognostic variables considered. The following variables were included in the model: treatment assigned at randomization, age (in 5 groups: <50, 50–60, 60–65, 65–70, >70), history of hypertension, history of diabetes, heart rate, systolic and diastolic blood pressure, and Killip class (2 classes: 1 vs. >1), and hours between onset of symptoms and admission (in 3 groups: within 3 h, 4–6 h, >6 h). The

presence of significant interactions between treatment and prognostic factors was assessed by including in the model the appropriate interaction terms. All p values were two-sided. Because no evidence of interaction was found between treatment and any of the variables considered, and the results of multivariate analyses closely reflected those of the univariate ones, only the latter analyses are presented.

*Interim Analysis*

No interim analysis had been planned. However, in July 2002, when less than 2,300 patients had been randomized and the enrollment of patients into the study was proceeding very slowly, the Steering Committee considered the possibility of an early closure of the study. In order to base this decision on objective information, it was decided to conduct an interim analysis in order to estimate the probability that the study, if continued to its planned sample size, would show a significant difference in favor of the experimental arm, conditional on the results available at the time of the analysis. In contrast to standard interim analyses, this technique, commonly referred to as 'conditional power' [19], does not require any correction of the significance level, because it leads to early termination of the study, only if the results are to be considered negative. Because of this aim, in order not to jeopardize the collection of information in a blinded fashion for patients who had not yet terminated their follow-up, analysis was limited to the 2,047 patients enrolled before July 31, 2001.

By August 31, 2002, 206 events had been recorded, 107 in the placebo group and 99 in the carnitine group, for a cumulative 6-month incidence of 10.5 and 9.7%, respectively (p = 0.54). Although the observed 8% relative reduction in the incidence of the primary end point did not allow to definitely rejecting the hypothesis that *L*-carnitine is truly associated with the target 20% reduction, conditional power analyses indicated that the study had little probability to provide statistically significant evidence of an effect of *L*-carnitine, even if its final sample size was substantially increased. Indeed, to attain a power close to 80% the final sample size had to increase to more than 5,600 patients. The Steering Committee decided to terminate the study because interim results failed to provide evidence for a more than marginal effect of *L*-carnitine on the combined end point; given the fading rate of patients' randomization into the study, the enrolment of 3,000 more patients within a reasonable time period was considered unrealistic. Treatment codes were unblinded once the Steering Committee decided that patient's enrollment had to be terminated (see below in the Results section), on December 15, 2002, when 2,330 patients had been enrolled. Subsequently, in May 2003, survival data were updated, for those patients with follow-up data shorter than 6 months, by contacting the treating physician or the Municipality of residence. SPSS 9.0 statistical package was used for all statistical procedures.

## Results

Between June 24, 1997 and December 15, 2002, 2,330 patients were enrolled by 153 participating centers, 1,168 in the experimental arm and 1,162 in the placebo arm. One center randomized only 1 patient, assigned to placebo, and then refused any further collaboration, including the provision of baseline and follow-up data on this patient, excluded from all analyses. The two groups of patients were well matched with regard to baseline characteristics. Demographic and clinical characteristics of the study population by treatment arm are shown in table 1. Participants were mainly men (78%) with a mean age of 61 years. Before their index events, 8.8% had a myocardial infarction and 10.5% had previously undergone coronary revascularization by either coronary artery bypass surgery (8.8%) or percutaneous coronary angioplasty (1.7%). Sixteen percent had diabetes, 44% were current smokers, 41.1% had a history of hypertension and 34% of hypercholesterolemia; 14.9% were in Killip class $\geq 2$. The mean time from the onset of symptoms to study treatment administration was 5.3 h in both groups. The in-hospital treatments are reported in table 2. Notably, 77.4% of the patients received thrombolytic treatment and 79 and 68% were being treated with angiotensin-converting enzyme inhibitors and beta-blockers, respectively.

During the 6-month follow-up, the primary end-point, as defined by the number of patients who died plus the number of surviving patients with heart failure, was not significantly different between *L*-carnitine and placebo group (p = 0.27). The cumulative incidence curves are shown in figure 1.

**Table 1.** Baseline characteristics

| | Placebo (n = 161) | *L*-carnitine (n = 1,168) |
|---|---|---|
| Age, years | 61.4 ± 0.31 | 61.1 ± 0.32 |
| Male sex (%) | 913 (78.6) | 919 (78.7) |
| History of diabetes (%) | 197 (16.9) | 189 (16.2) |
| History of hypertension (%) | 480 (41.4) | 479 (41) |
| Smoking (%) | 497 (42.8) | 537 (46) |
| History of hypercholesterolemia (%) | 395 (34) | 397 (34) |
| Prior myocardial infarction (%) | 110 (9.5) | 93 (8) |
| Prior percutaneous coronary intervention (%) | 23 (2.0) | 12 (1.5) |
| Prior coronary bypass surgery (%) | 110 (9.5) | 93 (8.1) |
| Killip class (%) | | |
| I | 987 (85) | 993 (85) |
| II | 139 (12) | 128 (11) |
| III/IV | 35 (3) | 47 (4) |
| Time from onset of symptoms to study treatment, h | 5.3 ± 0.1 | 5.26 ± 0.11 |

None of the differences between groups were significant.

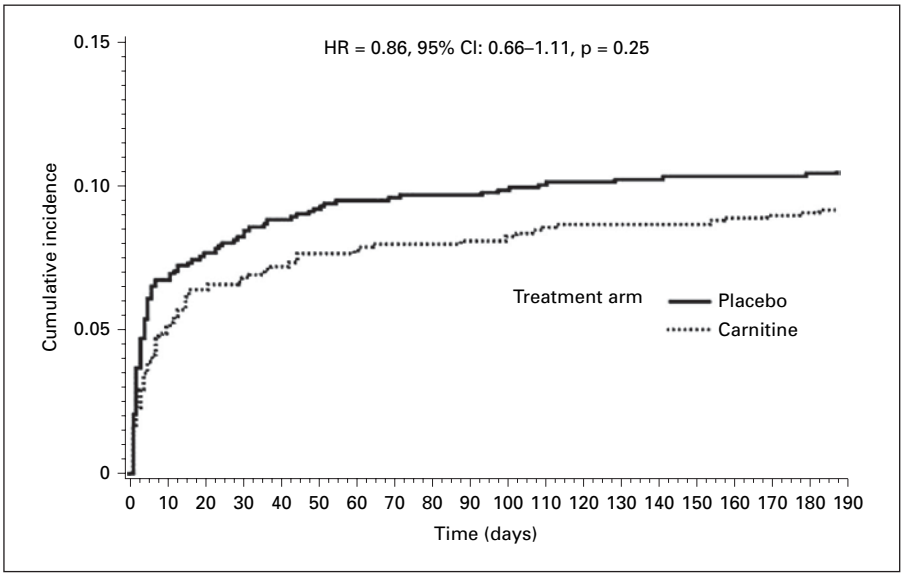


**Fig. 1.** Kaplan-Meier curve showing cumulative incidence of combined death and heart failure during 6-month follow-up in *L*-carnitine and control group.

**Table 2.** In-hospital treatments

| | Placebo (n = 1,161) | *L*-carnitine (n = 1,168) |
|---|---|---|
| Thrombolysis (%) | 893 (76.9) | 911 (78.0) |
| Aspirin (%) | 1,058 (91) | 1,065 (91.2) |
| Other antiplatelet agents | 200 (17.2) | 222 (19) |
| Angiotensin-converting enzyme inhibitors (%) | 917 (78.9) | 920 (78.8) |
| Beta-blockers (%) | 799 (68.8) | 786 (67.3) |
| Heparin (%) | 779 (67) | 769 (65.8) |
| Nitrates (%) | 1,009 (86.8) | 1,015 (86.9) |
| Digitalis (%) | 74 (6.4) | 60 (5.1) |
| Diuretics (%) | 424 (36.5) | 417 (35.7) |
| Calcium-antagonists (%) | 91 (7.8) | 88 (7.5) |
| Percutaneous coronary intervention (%) | 138 (11.9) | 127 (10.9) |
| Coronary bypass surgery (%) | 6 (0.5) | 6 (0.5) |
| Statin (%) | 900 (77.5) | 899 (76.9) |

None of the differences between groups were significant.

**Table 3.** Cumulative mortality at various time from randomization

| Days | Placebo | | *L*-carnitine | | Hazard ratio (95% CI) | p |
|---|---|---|---|---|---|---|
| | n | % | n | % | | |
| 0–5 | 44 | 3.8 | 27 | 2.3 | 0.61 (0.37–0.98) | 0.041 |
| 0–7 | 46 | 4.0 | 31 | 2.7 | 0.66 (0.42–1.05) | 0.083 |
| 0–15 | 50 | 4.3 | 42 | 3.6 | 0.83 (0.54–1.26) | 0.396 |
| 0–30 | 59 | 5.1 | 47 | 4 | 0.78 (0.53–1.16) | 0.234 |
| 0–60 | 66 | 5.7 | 55 | 4.7 | 0.82 (0.56–1.18) | 0.305 |
| 0–90 | 68 | 5.9 | 59 | 5.1 | 0.85 (0.60–1.22) | 0.412 |
| 0–180 | 75 | 6.5 | 67 | 5.7 | 0.88 (0.63–1.24) | 0.489 |

When the effect of the experimental treatment was evaluated separately in patients in Killip class I at admission (n = 1,980) and in patients in Killip class >1 (n = 349), the effect appeared to be concentrated in the larger group of patients in class 1 (HR = 0.83, 95% CI 0.6–1.13, p = 0.20), whereas no effect was seen in patients in class >1 (HR = 1, 95% CI 0.63–1.59, p = 0.99).

At multivariate analysis, the following variables were significant predictors of outcome (6-month incidence of the primary end point: History of diabetes ($p < 0.001$), of hypercholesterolemia (p = 0.005), of MI (p = 0.001), of bypass (p = 0.001) age ($p < 0.001$) and Killip class at admission ($p < 0.001$). Multivariate HR for treatment was 0.87 (95% CI: 0.67–1.13, p = 0.31).

*Analyses of Mortality*

At 6 months, 142 patients had died, 75 in the placebo group and 67 in the *L*-carnitine group, with a cumulative 6-month mortality rate of 6.5 and 5.7%, respectively, for a non-significant 12% reduction in mortality (p = 0.48). However, the difference in mortality was concentrated in the early period following randomization (table 3).

The secondary end-point of trial, reduction in mortality at 5 days from randomization, was significantly re-

duced in the *L*-carnitine arm (HR = 0.61, 95% CI 0.37–0.98, p = 0.041) (table 3). The difference in mortality decrease in the following period with mortality rate from day 7 to day 180 was similar in the two groups (table 3).

The rates of adverse events did not differ between patients assigned to *L*-carnitine or placebo. In none of the patients treatment was interrupted because of adverse events. The overwhelming majority of the reported serious adverse events were related to disease progression or complications. The rates of adverse events unrelated to the underlying disease did not differ between the patient groups.

## Discussion

Both experimental and clinical studies have clearly shown that during prolonged and total myocardial ischemia necrosis progressively involves the full thickness of myocardium [20–21] and that the extent of myocardial salvage and residual LV function represent the most powerful determinants of survival after AMI [22].

However, despite considerable progresses in both pharmacological and interventional therapies, mortality after AMI still remains high. This is the result not only of the organizational difficulties in reducing the time interval from beginning of transmural myocardial ischemia and infarct-related artery recanalization (and consequent myocardial salvage), but also of the deleterious effects of the reperfusion damage consequent to infarct-related artery recanalization, that at least in part abolish the beneficial effect of acute blood supply to the ischemic myocardium [23].

In this scenario it would be extremely useful to adopt therapeutic strategy capable of achieving the following goals: (1) time interval reduction between onset of chest pain and 'needle' or 'balloon', (2) protection of myocardium through the prolonged ischemia before reperfusion occurs, (3) protection of myocardium from the 'reperfusion damage'. The last two results can be achieved by therapeutic strategies aimed at 'protecting' the myocardium during both the ischemia and reperfusion phase [24]. These two last goals can be achieved by appropriate metabolic interventions; in fact, both experimental and clinical studies have demonstrated the beneficial functional and clinical effect of a therapy based on solid metabolic fundamentals [23].

### *Rational and Results of CEDIM 1 and 2 Trials*

During AMI, plasma free fatty acid levels rapidly increase and exert a relevant toxic effect to the ischemic myocardium causing increase in membrane damage and consequent cell swelling and microvascular compression, arrhythmias, metabolic inefficiency with consequent myocardial function deterioration [25]. Carnitine is the main factor that determines the turnover of the fatty acids in the mitochondria. During prolonged ischemia carnitine depletion rapidly occurs [25] and its exogenous administration may exert an important beneficial mechanical effect by several mechanisms: infarct size reduction within the risk area [26], improved functional recovery of post-ischemic dysfunctioning myocardium [27] and, lastly, limitation of the deleterious phenomenon of post-MI LV remodeling [28]. Based on these data, we performed the CEDIM 1 trial whose aim was that of verifying the effects of acute and chronic *L*-carnitine administration on LV remodeling in patients with first, anterior AMI [17]. In this multicenter trial, progressive increase (3, 6 and 12 months observation) in both end-diastolic and end-systolic volumes was significantly attenuated in patients treated with *L*-carnitine in comparison to those treated with placebo in adjunction to standard treatment. Since end-systolic volume increase is a major powerful predictor of survival after AMI [22], and therapeutic strategies aimed at attenuating LV remodeling are effective in reducing mortality after anterior AMI, the CEDIM 2 trial was designed and performed in order to verify the clinical benefit of *L*-carnitine treatment after AMI. In CEDIM 2 trial a non-significant 14% reduction in the incidence of the primary end point, i.e. the combined occurrence at 6 months of death and heart failure, was observed in the *L*-carnitine arm. In the light of unsatisfactory probability that the study would provide statistically significant evidence (partly because of the lower than foreseen cumulative incidence of end points and of the slow rate of enrolment) it was decided to interrupt patients' accrual before the target sample size of 4,000 patients. The effect of *L*-carnitine on secondary prespecified end point was of interest and, in our opinion, deserves attention. In fact, in patients treated with intravenous *L*-carnitine mortality was reduced in the first 5 days: 27 deaths in the carnitine arm vs. 44 in the placebo arm (HR = 0.61, 95% CI 0.37–0.98, p = 0.041). The mortality reduction was mostly concentrated in the very acute phase of MI and was diluted thereafter since mortality from day 7 through follow-up was similar in the two groups of patients. Such an effect on early mortality induced us to reanalyze the results of the CEDIM 1 trial that was designed and performed to

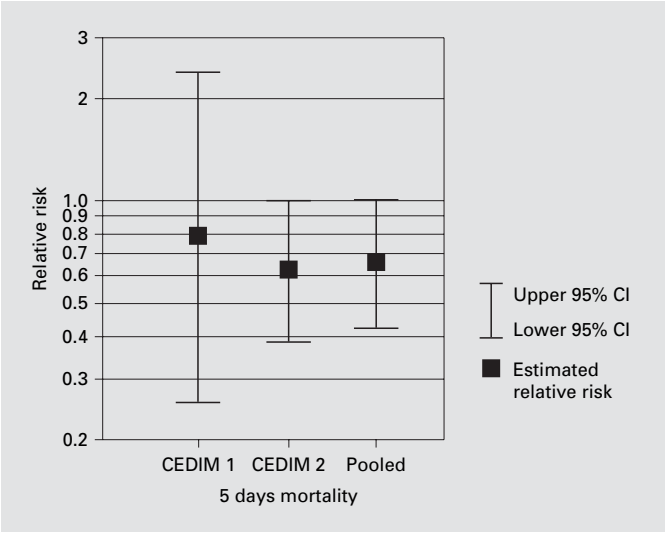


**Fig. 2.** Estimated relative risk reduction in mortality at 5 days from randomization in CEDIM 1, CEDIM 2 and in pooled analysis. CI = Confidential index.

investigate the effects of *L*-carnitine on post-MI LV remodeling. Interestingly, the time course and entity of the reduction of mortality shown by the CEDIM 2 trial closely mirrored those of the CEDIM 1 trial. If the results of the two studies are pooled, using standard meta-analytic techniques (fig. 2), the suggestion of an effect of *L*-carnitine on early mortality is reinforced.

*Metabolic Treatment of Acute Myocardial Infarction: Mechanisms of Action and Clinical Implications*

The results of CEDIM 2 trial closely resemble those of the GIK study [8] performed in patients undergoing primary PTCA. As in CEDIM 2, the reduction in mortality observed in the GIK study in primary PTCA was concentrated in the first 5 days. The beneficial functional, and consequently clinical, effects of metabolic treatment are likely due to the attenuation of regional and global LV deterioration caused by the extent of irreversible myocardial damage provoked by prolonged myocardial ischemia. Beneficial effects of metabolic intervention in AMI are very likely not limited to the protection of the ischemic myocardium in the very acute phase of ischemia and reperfusion, but also involve protection of the acutely overloaded non-infarcted region of the ventricle. In an elegant experimental model of myocardial infarction caused by permanent ligation of the left anterior descending coronary artery and 50% stenosis of the circumflex coronary artery (a model resembling AMI in multivessel coronary artery disease), metabolic treatment with GIK was effective in abolishing functional deterioration of viable myocardium in the remote region, and also in preventing deterioration of global LV function, thus avoiding the development of progressive LV power failure [29].

*Limitations of the CEDIM 2 Trial*

The most important shortcoming of the CEDIM 2 trial is represented by the fact that the reduction in early mortality did not represent the primary end point of the study; thus, a new trial, specifically addressed at evaluating the effect of *L*-carnitine on early mortality after acute myocardial infarction, should be designed and performed to further support the CEDIM 2 results as well as the CEDIM 1-CEDIM 2 pooled analysis and to exclude the possibility of a chance finding. Furthermore, in CEDIM 2 trial the administration of *L*-carnitine was prolonged for 6 months; the results of the study clearly indicated that the benefit was concentrated in the very early phase, thus suggesting that *L*-carnitine administration is particularly effective in the first week after anterior AMI.

## Conclusions

As was the case for other treatments subsequently demonstrated as effective, there is initial stuttering evidence that metabolic therapy may improve survival in AMI. In CEDIM 2 trial *L*-carnitine therapy led to a reduction in early mortality without affecting the risk of death and heart failure at 6 months in patients with anterior AMI. Further studies should be designed and performed to further support the CEDIM 2 results as well as the CEDIM 1-CEDIM 2 pooled analysis in the perspective of a 'new' therapeutic strategy for AMI based on the administration of *L*-carnitine as soon as possible after the acute event.

## Acknowledgment

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## Appendix

*CEDIM 2 Study Organization*

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