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ORIGINAL ARTICLE

L-Carnitine in the Secondary Prevention of Cardiovascular Disease: Systematic Review and Meta-analysis

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Abstract

Objective: To evaluate the effects of L-carnitine compared with placebo or control on morbidity and mortality in the setting of acute myocardial infarction.

Methods: A systematic review and meta-analysis of 13 controlled trials (N=3629) was conducted to determine the effects of L-carnitine vs placebo or control on mortality, ventricular arrhythmias (VAs), angina, heart failure, and reinfarction. These trials were identified via searches of the Ovid MEDLINE, PubMed, and Excerpta Medica (Embase) databases between May 1, 2012, and August 31, 2012.

Results: Compared with placebo or control, L-carnitine was associated with a significant 27% reduction in all-cause mortality (odds ratio, 0.73; 95% CI, 0.54-0.99; *P*=.05; risk ratio [RR], 0.78; 95% CI, 0.60-1.00; *P*=.05), a highly significant 65% reduction in VAs (RR, 0.35; 95% CI, 0.21-0.58; *P*<.0001), and a significant 40% reduction in the development of angina (RR, 0.60; 95% CI, 0.50-0.72; *P*<.00001), with no reduction in the development of heart failure (RR, 0.85; 95% CI, 0.67-1.09; *P*=.21) or myocardial reinfarction (RR, 0.78; 95% CI, 0.41-1.48; *P*=.45).

Conclusion: Compared with placebo or control, L-carnitine is associated with a 27% reduction in all-cause mortality, a 65% reduction in VAs, and a 40% reduction in anginal symptoms in patients experiencing an acute myocardial infarction. Further study with large randomized controlled trials of this inexpensive and safe therapy in the modern era is warranted.

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Although therapies for acute coronary syndrome (ACS), including percutaneous coronary intervention, dual antiplatelet therapy, β-blockers (BBs), statins, angiotensin-converting enzyme inhibitors (ACEIs), omega-3 fatty acids, and cardiac rehabilitation,[1] have markedly improved clinical outcomes, adverse cardiovascular (CV) events still occur too frequently after ACS. One promising therapy for improving cardiac health involves using L-carnitine to improve free fatty acid levels and glucose oxidation.[2] 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).

L-Carnitine, a quaternary amine, plays an important role in energy production in the myocardium and has been shown to transport free fatty acids into the mitochondria, thus increasing the preferred substrate for oxidative metabolism in the heart.[2] Moreover, L-carnitine has been shown to prevent fatty acid ester accumulation that occurs during ischemic events, which may lead to fatal ventricular arrhythmias (VAs).[2,3] As myocardial carnitine levels are quickly diminished during an ischemic event, exogenous supplementation with L-carnitine has been shown to replenish depleted myocardial carnitine levels and improve cardiac metabolic and left ventricular (LV) function.[4-7] Furthermore, compared with placebo, a meta-analysis of 4 studies demonstrated a significant reduction in LV dilation in the first year after an AMI with the use of L-carnitine.[8] The prevention of LV dilation and the preservation of cardiac function after an AMI is, indeed, clinically important, as LV dilation is a powerful predictor of progression to heart failure (HF) and death.[9]

Thus, we sought to determine the effects of L-carnitine compared with placebo or control in patients experiencing an AMI by performing a systematic review and meta-analysis of available studies.

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METHODS

We performed a systematic review of the available literature according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines for the conduct of systematic reviews of intervention studies.[10]

Data Sources and Searches

Studies were identified through searches of the following sources: Ovid MEDLINE (1974-2012), PubMed (1973-2012), and Embase (1974-2012). To identify further potentially relevant studies missed by the electronic database search, reference lists from identified trials and review articles were manually screened. Searches were restricted to English language and were updated using automated weekly email alerts between May 1, 2012, and August 31, 2012. Supplemental Appendix 1 (available online at http://www.mayoclinicproceedings.org) provides full details of the search strategies. Supplemental Appendix 2 (available online at http://www.mayoclinicproceedings.org) provides full details of the excluded trials.

Study Selection

Studies were selected for inclusion on the basis of the following criteria: comparative trials of adults (≥18 years old) receiving L-carnitine compared with placebo or control, with outcomes of all-cause mortality, CV events (including myocardial reinfarction), and development of HF and VAs. We excluded studies that did not report mortality or morbidity outcomes. The titles and abstracts of studies identified by the search strategy were independently screened by 2 reviewers (J.J.D. and H.F.), and clearly irrelevant studies were discarded.

Data Extraction and Quality Assessment

The following data elements were extracted from each study: the number of patients per arm, the nature of the intervention, patient inclusion criteria, baseline and follow-up blood pressure, heart rate, ejection fraction, type of AMI index event (percentage anterior, percentage inferior, etc), and duration of follow-up. The following outcomes were also extracted from each trial: all-cause mortality, CV events (myocardial reinfarction), and development of HF and VAs. Quality assessment was judged according to the following criteria: concealment of treatment allocation; similarity of both groups at baseline regarding prognostic factors and medication use; blinding of outcome assessors, care providers, and patients; completeness of follow-up; and intention-to-treat analysis. Overall study quality was quantified using the Jadad score.[11] Data extraction was performed by 3 independent reviewers (J.J.D., H.F., and A.R.M.), and quality assessment was undertaken using standardized pro forma by 2 independent reviewers (H.F. and A.R.M.). Risk of bias was assessed using criteria recommended by the Cochrane Collaboration specifically evaluating sequence generation of allocation; allocation concealment; blinding of participants, staff, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Trials with high or unclear risk of bias for the first 3 criteria were considered to be at high risk for bias, and the remaining trials were considered to be at low risk for bias.

Data Synthesis and Analysis

We express outcome results for each study as a risk ratio (RR) or odds ratio (OR) (95% CI). Summary estimates were computed using a DerSimonian and Laird random-effects meta-analysis model. We report pooled results as an RR or OR and number needed to treat (NNT). Statistical heterogeneity across trials was estimated using the I^2 statistic,[12] with $I^2<30\%$ denoting low heterogeneity; $I^2=30\%$-50%, moderate heterogeneity; and $I^2>50\%$, substantial heterogeneity.[13] A 2-tailed $P<.05$ was considered statistically significant for all the analyses. Cochrane Review Manager (RevMan v.5) software was used for all the analyses. A sensitivity analysis was conducted to consider the overall effect of studies with a moderate number of events (≥10 events).

RESULTS

Identification and Selection of Studies

The literature search yielded 153 titles, of which 18 were reviewed in full text on the basis of the inclusion criteria. Of these, 13 studies were deemed eligible for inclusion (Figure 1).[4,14-25] Supplemental Tables 1 and 2 (available online at http://www.mayoclinicproceedings.org) summarize the characteristics of the included studies and the risk of bias in the included trials.[4,14-25] Supplemental Table 3 (available online at http://

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www.mayoclinicproceedings.org) summarizes the quality of the included trials.[4,14-25]

Characteristics of Included Studies

All the trials were comparison trials of L-carnitine compared with placebo or control in the AMI setting. All the background medications and baseline characteristics were statistically similar between the comparison groups in each trial except for that by De Pasquale et al.[15] Trials enrolled a median of 96 patients (interquartile range, 20-2329 patients), with median follow-up of 2 months (interquartile range, 0.7-12 months).

Quality Assessment

Six studies scored well on the methodological quality indicators (Supplemental Table 3 available online at http://www.mayoclinicproceedings.org). Concealed allocation and blinding of at least 1 outcome assessment was stated in 7 and 9 of the 13 trials, respectively.

Study Outcomes

All-Cause Mortality. Eleven trials (n=3579) reported on all-cause mortality. There was a significant 27% reduction in all-cause mortality with L-carnitine compared with placebo or control (odds ratio, 0.73; 95% CI, 0.54-0.99; P=.05; I^2=4% [Figure 2]; RR, 0.78; 95% CI, 0.60-1.00; P=.05; I^2=0%). The NNT over the course of the trials was 38 (95% CI, 23-105).

Ventricular Arrhythmias. Five trials (n=229) reported on VAs. Compared with placebo or control, L-carnitine was associated with a highly significant 65% reduction in VAs (RR, 0.35; 95% CI, 0.21-0.58; P<.0001; I^2=0%) (Figure 3). The NNT over the course of the trials was 4 (95% CI, 3-6). High-grade ventricular premature beats on day 2 were used by Martina et al[20] and Rizzon et al[4] for calculation of VA events.

Myocardial Reinfarction. Four trials (n=829) reported on myocardial reinfarction. Compared with placebo or control, L-carnitine was not associated with a reduction in myocardial reinfarction (RR, 0.78; 95% CI, 0.41-1.48; P=.45; I^2=0%) (Figure 4).

Heart Failure. Six trials (n=3214) reported on the development of HF. Compared with placebo or control, L-carnitine was not associated with a reduction in the development of HF (RR, 0.85; 95% CI, 0.67-1.09; P=.21; I^2=0%) (Figure 5).

Anginal Attacks. Two trials (n=261) reported on the development of angina. Compared with placebo or control, L-carnitine was associated with a 40% reduction in the development of angina (RR, 0.60; 95% CI, 0.50-0.72; P<.00001; I^2=0%) (Figure 6). The NNT over the course of the trials was 3 (95% CI, 2-5).

Sensitivity Analysis

Excluding the 5 smallest studies,[4,17,18,22,25] trials including a moderate number of mortality events (≥10 events total) indicated a 34% reduction in all-cause mortality with L-carnitine compared with placebo or control (RR, 0.67; 95% CI, 0.42-1.07; P=.09; I^2=40%) (Figure 7).

DISCUSSION

This systematic review of 13 controlled trials in 3629 patients involving 250 deaths, 220 cases of new HF, and 38 recurrent myocardial infarctions found that the use of L-carnitine was associated with a significant reduction in all-cause

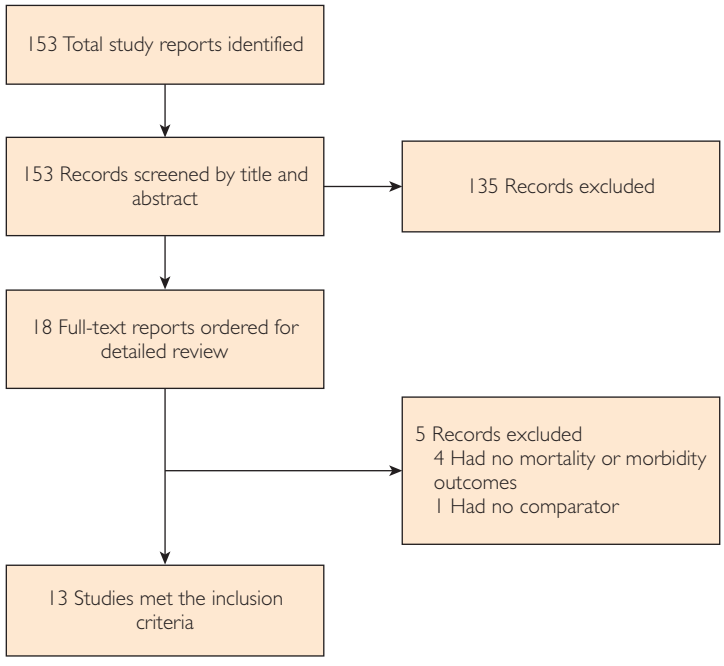

FIGURE 1. Process for selecting included trials.

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,[15] 1990	0	49	18	97	1.2	0.04 (0.00-0.74)
Davini et al,[14] 1992	1	81	10	79	2.1	0.09 (0.01-0.69)
Jacoba et al,[18] 1996	0	22	1	17	0.9	0.24 (0.01-6.39)
Rebuzzi et al,[22] 1984	0	12	1	10	0.8	0.25 (0.01-6.94)
Xue et al,[25] 2007	0	48	1	48	0.9	0.33 (0.01-8.22)
Iyer et al,[17] 1999	1	30	2	30	1.5	0.48 (0.04-5.63)
Singh et al,[23] 1996	4	51	6	50	5.1	0.62 (0.17-2.36)
Kobulia et al,[19] 2002	4	45	7	53	5.4	0.64 (0.17-2.35)
Iliceto et al,[16] 1995	21	233	27	239	22.8	0.78 (0.43-1.42)
Tarantini et al,[24] 2006	67	1168	75	1161	57.0	0.88 (0.63-1.24)
Rizzon et al,[4] 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: Tau^2=0.01; χ^2=10.36, *df*=10 (*P*=.41); I^2=4%
Test for overall effect: *Z*=2.00 (*P*=.05)

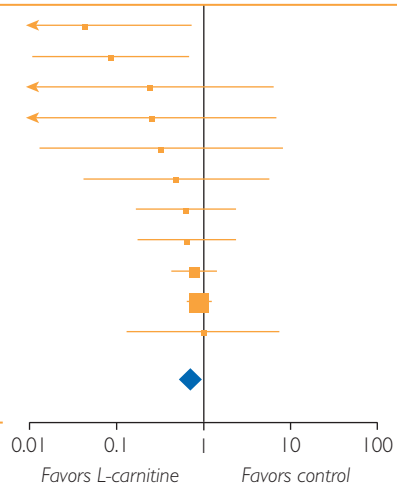

FIGURE 2. Forest plot of odds ratios for all-cause mortality. IV = inverse variance.

mortality and a highly significant reduction in VAs and anginal attacks.

The potential mechanisms responsible for the observed beneficial impact of L-carnitine in AMI are likely multifactorial and may, in part, be conferred through the ability of L-carnitine to improve mitochondrial energy metabolism in the heart by facilitating the transport of long-chain fatty acids from the cytosol to the mitochondrial matrix, where β-oxidation occurs, removing toxic fatty acid intermediates, reducing ischemia induced by long-chain fatty acid concentrations, and replenishing depleted carnitine concentrations seen in ischemic, infarcted, and failing myocardium.[2-4,26-29] Moreover, L-carnitine has been shown to have beneficial effects on LV remodeling, with a significant reduction in LV volumes after AMI.[16] L-Carnitine has been shown to reduce infarct size (measured by reductions in cardiac enzymes) in numerous AMI clinical trials, leading to improvements in myocardial viability and salvage.[18,22,23] Furthermore, L-carnitine has been shown to significantly reduce VAs after AMI, which may partly explain the early significant 39% reduction in 5-day mortality (a prespecified secondary end point) in the Carnitine Ecocardiografia Digitalizzata Infarto Miocardico 2 (CEDIM 2) trial[24] (27 events

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,[4] 1989	2	28	13	28	13.6	0.15 (0.04-0.62)
Pehlivanoglu et al,[21] 1996	1	12	9	18	7.1	0.17 (0.02-1.15)
Rebuzzi et al,[22] 1984	0	12	1	10	2.8	0.28 (0.01-6.25)
Martina et al,[20] 1992	4	12	7	8	37.2	0.38 (0.16-0.88)
Singh et al,[23] 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: Tau^2=0.00; χ^2=2.61; *df*=4 (*P*=.63); I^2=0%
Test for overall effect: *Z*=4.03 (*P*<.0001)

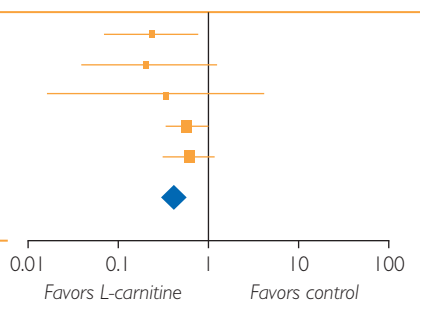

FIGURE 3. Forest plot of risk ratios for ventricular arrhythmia. IV = inverse variance.

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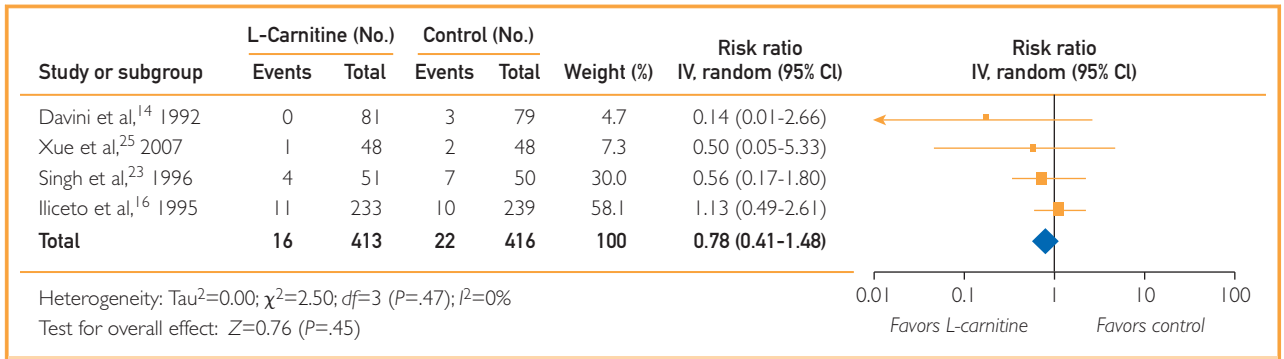

FIGURE 4. Forest plot of risk ratios for myocardial reinfarction. IV = inverse variance.

vs 44 events; hazard ratio, 0.61; 95% CI, 0.37-0.98; *P*=.041).[4,20-24]

These findings suggest that L-carnitine may reduce all-cause mortality, VAs, and anginal attacks in patients with AMI. Current therapy for angina includes revascularization, along with BBs, calcium channel blockers, and nitrates, with a new class of sodium channel blockers (ranolazine) recently added to this list. This newest therapy, ranolazine, may effectively improve symptoms but thus far, unlike L-carnitine, does not seem to reduce clinical events, and only limited data support event reduction with calcium antagonists and nitrates. Although current ACS/AMI guidelines do not include L-carnitine, substantial evidence, discussed previously herein, seems to support that a larger, multicenter trial should be performed to verify the benefit of L-carnitine in AMI[1] and in stable angina. Although a large, randomized, multicenter trial is required to confirm the results of this systematic review, considering its low cost and excellent safety profile, L-carnitine therapy could be currently considered in selected patients with high-risk or persistent angina after AMI who cannot tolerate ACEI or BB therapy.

Several important potential study limitations should be considered. First, not all the trials included in this meta-analysis were double blind (n=5), with 6 of the 13 included trials being rated as moderate or good in quality (ie, Jadad score ≥3 of 5). Second, most trials included a relatively small number of patients, except the CEDIM 2 trial[24] (n=2329), which contributed approximately 62% of the mortality events in the included trials. However, an analysis of the entire data set showed no heterogeneity between trials for mortality (I^2=4%), VAs (I^2=0%), anginal attacks (I^2=0%), HF, and myocardial reinfarction (I^2=0%). Moreover,

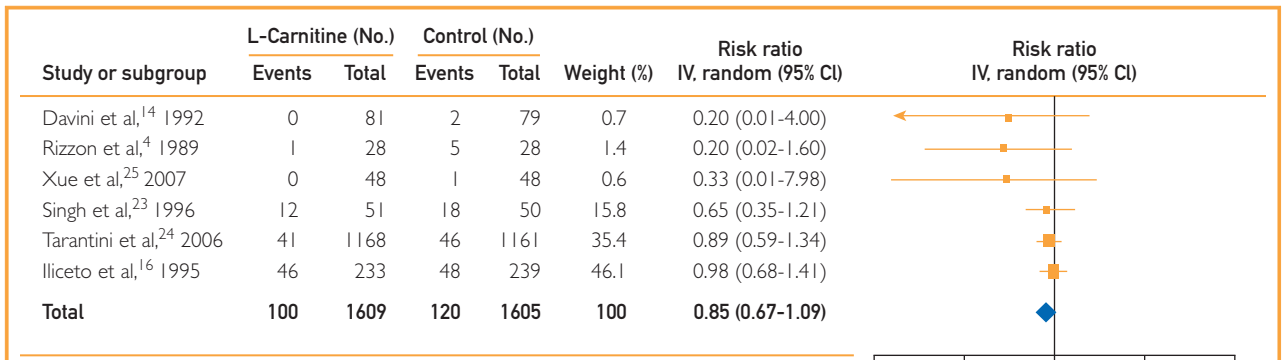

FIGURE 5. Forest plot of risk ratios for the development of HF. IV = inverse variance.

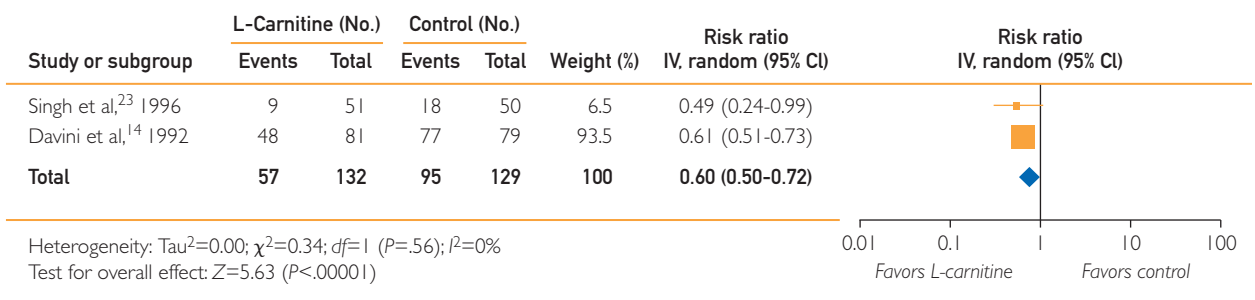

FIGURE 6. Forest plot of risk ratios for the development of angina. IV = inverse variance.

it is possible that this systematic review missed significance for the outcomes of development of HF and myocardial reinfarction, as Kobulia et al[19] reported a 43.5% reduction in cases of HF after 6 months and a 15% reduction in myocardial reinfarction or death, of which the number of outcomes between groups could not be obtained. Moreover, most of the data were collected with L-carnitine before the current era, particularly combining revascularization with dual antiplatelet therapy and high-dose potent statins. Certainly, other therapies, including omega-3 fatty acids or fish oils, seemed very beneficial in an era with less intensive treatment (the Diet and Reinfarction Trial and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Prevenzione trial),[30,31] whereas these benefits are blunted or have disappeared completely in the current, more aggressive era (the Investigators in the Outcome Reduction with Initial Glargine Intervention and the Supplementation with Folate, Vitamin B6 and B12, and/or Omega-3 Fatty Acids trial).[32,33] However, the CEDIM 2 trial studied L-carnitine in addition to current optimal medical therapy (thrombolysis [78%], aspirin [91%], ACEIs [79%], BBs [68%], heparin [67%], percutaneous coronary intervention [12%], and statins [77%]) and showed a significant reduction in the predefined secondary end point of 5-day mortality (P=.041). Despite the early mortality reduction seen (perhaps due to the high number of deaths occurring early on), the CEDIM 2 trial did not recruit its target goal of 4000 or more patients (only 2330 were enrolled) and may have been underpowered to show a difference on CV outcomes over the trial duration.[24] Thus, the potential benefits of L-carnitine will need to be reassessed in the current era in an appropriately powered trial. Also, as in most such meta-analyses, several dosages (2-14 g/d), intervals (1, 2, and 3 times daily), and formulations (intravenous, bolus or infusion, and by mouth) were used. From the clinical trials, a minimal effective dose seems to be 2 g/d of L-carnitine, with optimal dosing of approximately 6 to 9 g/d. Finally, some could question the reliability of one of the included published studies,[23] although this study has never officially been involved in any retraction.[34] Nevertheless, excluding this study only slightly lowers the benefit on total mortality (−26%; P=.07; I^2=7%) and does not affect the benefit on VAs (−72%; P=.0001; I^2=0%), but the effect on angina could no longer be adequately assessed.

Despite these potential study limitations, we believe that 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 potentially for angina, and advocate for a larger trial to be performed in the AMI setting to confirm these results in the modern era of routine revascularization and other intensive medical therapies. However, a large trial may never be performed because L-carnitine is an over-the-counter supplement available to the public, which decreases the potential revenue compared with a synthesized product. Although L-carnitine therapy has been under discussion for some time, most trials were small and did not have a robust number of hard end points. Moreover, the CEDIM 2 trial, having 142 mortality events, was generally viewed as being a "negative" trial, despite a significant reduction in 5-day mortality seen with L-carnitine. However, the present meta-analysis was able to combine 11 trials

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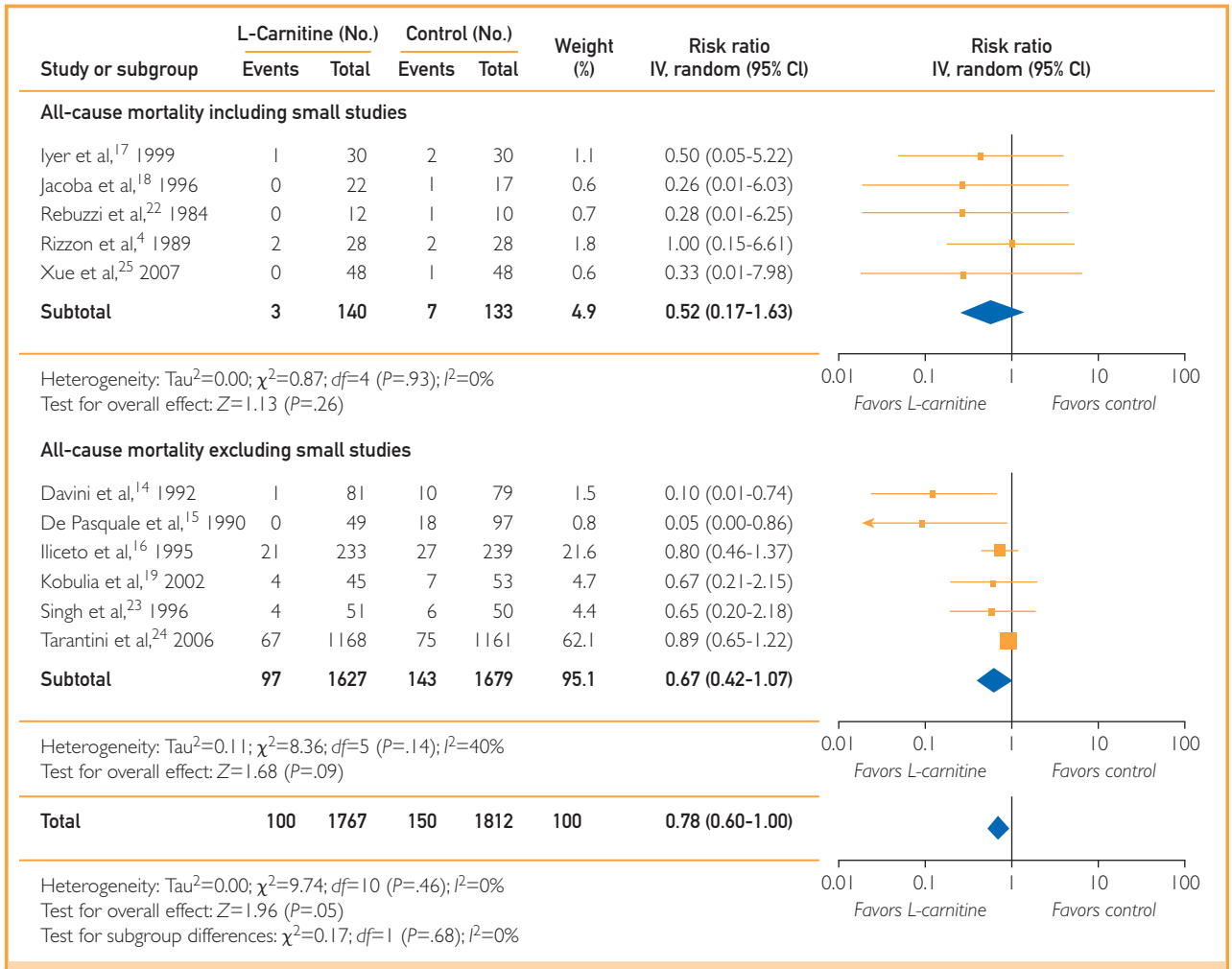

FIGURE 7. Forest plot of risk ratios for all-cause mortality including and excluding small studies. IV = inverse variance.

encompassing 250 mortality events and indicated a significant reduction in all-cause mortality with L-carnitine vs placebo or control for the secondary prevention of CV disease.

CONCLUSION

Compared with placebo or control, L-carnitine is associated with a 27% reduction in all-cause mortality, a 65% reduction in VAs, and a 40% reduction in anginal symptoms in patients experiencing an AMI. Further study with large randomized controlled trials of this inexpensive and safe therapy in the modern era is warranted.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

Abbreviations and Acronyms: **ACEI** = angiotensin-converting enzyme inhibitor; **ACS** = acute coronary syndrome; **AMI** = acute myocardial infarction; **BB** = β-blocker; **CEDIM 2** = Carnitine Ecocardiografia Digitalizzata Infarto Miocardico 2; **CV** = cardiovascular; **HF** = heart failure; **LV** = left ventricular; **NNT** = number needed to treat; **RR** = risk ratio; **VA** = ventricular arrhythmia

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