Regarding L-Carnitine and Cardiovascular Disease

To the Editor: We read with interest the recent meta-analysis performed by DiNicolantonio et al[1] on L-carnitine and cardiovascular disease published in the June 2013 issue of *Mayo Clinic Proceedings*, and we have several concerns regarding the analysis and conclusions.

Although the authors evaluated the quality of the included studies and reported their risk of bias, we believe that they underestimated this risk and that this body of evidence is, in fact, of very low quality. We also believe that the benefit reported is not believable, in part because it is greater than other well-studied interventions in cardiovascular disease.

Regarding the risk of bias, several of the weaknesses were noted by the authors. However, other weaknesses were not identified. Of the 13 articles included in the 5 meta-analyses performed, only 4 were definitely blinded to the patient, health care practitioner, and outcome assessor (Supplemental Table 3 in the article), and only 6 were of good quality by the authors' own criteria (Jadad score >2). The authors indicate in their Supplemental Table 1 that the articles by De Pasquale et al[2] and Davini et al[3] have "unclear bias risk." Both of these articles found a much greater effect of L-carnitine on mortality than the other articles in the meta-analysis. The article by De Pasquale et al[2] was not a randomized trial, and the investigators gave L-carnitine when it was "available." A study such as this is at high risk for bias and should not have been included in the meta-analysis. The study by Davini et al[3] was not blinded. Results indicate that postinfarction angina developed in 77 of the 79 patients in the control group, a proportion far greater than the literature reports in this situation.

This study also found that L-carnitine reduced heart rate, systolic blood pressure, and blood lipid levels—findings not reported elsewhere in the literature. Thus, this study is also at high risk for bias and should not have been included in the meta-analyses.

The authors acknowledged that there have been problems noted with research conducted by Dr Singh, but they rate the article by Singh et al[4] as the second highest-quality article in their meta-analysis. They included the article because Singh et al have not retracted their article. Dr Singh has not retracted any of his many articles, but when asked to produce his data for the *BMJ* he replied that they were "eaten by termites."[5] As a result, both the *Lancet* and the *BMJ* have retracted *all* the articles he has published in their journals. The *Postgraduate Medical Journal* (where the article on carnitine by Singh et al[4] cited by DiNicolantonio et al[1] was published) does not have the same resources as the *Lancet* to investigate fraud. It is clear from the article by White[5] in the *BMJ* (cited by the authors) that the investigators from the *BMJ* believe that Dr Singh's research is fraudulent. This article should not have been included in the meta-analyses.

The authors note that the article by Iliceto et al[6] had complete follow-up (Supplemental Table 3). This article studied the effect of L-carnitine on echocardiography after 1 year (negative study), not mortality. The authors of this study reported on mortality but made no effort to search death indexes. There were nearly as many dropouts as deaths, which suggests that, had death indices been searched, the results could have been considerably different.

The authors noted that 3 of their meta-analyses gave significant results. The angina meta-analysis had only 2 studies, one by Davini et al[3] and one by Singh et al.[4] This meta-analysis should not have been conducted because of the poor quality of these 2 articles. Furthermore, the number needed to treat for this meta-analysis is 3, which is difficult to believe (it far exceeds the benefits of β-blockers, angioplasty, and other currently used interventions). The analysis on clinically important ventricular arrhythmias examined 5 studies. The article by Singh et al[4] was the study with the highest weight. The 2 studies with significant results[7,8] examined the reduction in ventricular premature beats on day 2 after myocardial infarction, which is not considered a serious ventricular arrhythmia. The number needed to treat for this meta-analysis was 4, which is similarly extraordinarily low and difficult to believe.

The authors did not perform a sensitivity analysis based on study quality, which would have been helpful. The mortality analysis used the I^2 statistic and suggested low heterogeneity. This statistic is misleading with so many small studies. In fact, heterogeneity is likely in this analysis, considering that the χ^2 statistic for heterogeneity was greater than its degrees of freedom, which makes combining these studies concerning.[9]

As outlined above, there are too many flaws with the articles included in this systematic review to conclude that L-carnitine is associated with a 27% reduction in mortality, a 65% reduction in ventricular arrhythmias, or a 40% reduction in angina. Thus, it is premature to conclude from this weak evidence that "considering its low cost and excellent safety profile, L-carnitine could be considered in selected patients."

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In reply—Regarding L-Carnitine and Cardiovascular Disease

We thank Thompson et al[1] for their interest in our L-carnitine meta-analysis. Thompson et al claim that because the research performed by Davini et al[2] was not blinded, it should not have been included in our meta-analysis. However, blinding was not an inclusion criterion for our meta-analysis. In addition, 2 recently approved cardiovascular medications that are recommended for the treatment of acute coronary syndrome and the prevention of stroke in patients with atrial fibrillation (ticagrelor and dabigatran, respectively) were not definitively blinded in their landmark trials. Indeed, the Food and Drug Administration documents indicated that at least 452 patients in the ticagrelor trial (Platelet Inhibition and Patient Outcomes trial) became unblinded before the database lock, and 20% of the dabigatran trial (Randomized Evaluation of Long-Term Anticoagulant Therapy [RE-LY]) documents reviewed by the adjudication core committee were noted to contain text that could have potentially unblinded reviewers.[3,4]

Thus, stating that the trial by Davini et al[2] should not have been included in our meta-analysis does not seem relevant, especially because this trial was testing L-carnitine (a natural substance) and the study sponsor was not seeking approval for a potentially profitable branded medication (in which unblinding would undoubtedly be more of a concern).

In regard to including the trial by Singh et al,[5] we discussed in detail the issues alluded to by the authors. Specifically, we performed a sensitivity analysis that excluded this trial, which revealed a similar reduction in all-cause mortality with L-carnitine (26% reduction [P=.07] vs the overall conclusions, which indicated a 27% reduction [P=.05]). Moreover, Thompson et al claim that combining so many small studies could result in misleading conclusions. However, when we excluded the smaller trials, a similar reduction in all-cause mortality was still found with L-carnitine (23% reduction; P=.09).

Also, we strongly disagree with the assertion that the trial by Iliceto et al[6] should have been excluded because dropouts were nearly as high as deaths because dropouts have been significantly greater than deaths in large randomized controlled trials that have been used in the past as the foundation for approval of cardiovascular medications. Indeed, in the RE-LY trial, there was a significant and unequal dropout rate in both the dabigatran and warfarin groups (21% and 16.6%, respectively) that far exceeded the number of deaths.[4]

The authors also indicate that our meta-analysis on ventricular arrhythmias should not have included the trials by Martina et al[7] and Rizzon et al[8] because they used ventricular premature beats as end points, which Thompson et al stated are not considered severe arrhythmias. However, these 2 trials measured "high-grade" ventricular premature beats, which many would consider to be serious arrhythmias. Regardless, exclusion of both of those trials still indicates that L-carnitine causes a significant 59% reduction in ventricular arrhythmias (relative risk, 0.41; 95% CI, 0.20-0.85; P=.02). Nevertheless, we believe that our meta-analysis is considerably stronger regarding the mortality results compared with our findings on ventricular arrhythmias and angina, the latter of which, as we discussed, we would not be able to assess at all without including the trial by Singh et al.[5]

In summary, even after acknowledging the limitations that Thompson et al point out, L-carnitine still seems to offer potentially potent cardiovascular benefits, particularly regarding mortality benefits, in patients who have experienced an acute myocardial infarction. Although we appreciate the concerns regarding the limitations discussed by Thompson and colleagues, this debate cannot further be settled without an adequately powered, well-performed randomized controlled trial.

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