Oral L-arginine Supplementation in Acute Myocardial Infarction Therapy: A Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Objective: The objective was to analyze completed trials assessing the effect of oral L-arginine supplementation on clinical outcomes of patients with acute myocardial infarction (AMI).

Background: Prior trials suggest that oral L-arginine administration improves endothelial function in patients with stable coronary artery disease (CAD). However, it is still unclear whether oral supplementation of L-arginine has any effect on clinical outcomes in patients with unstable CAD, such as AMI.

Methods: We systematically searched PubMed, Cochrane Library, Embase, reviews, and reference lists of relevant articles. The search strategy paired the term "arginine" with the following: "coronary heart disease," "myocardial infarction," "cardiovascular disease," "ischemia," and "trial." We conducted a meta-analysis of randomized, placebo-controlled L-arginine supplementation trials that evaluated clinical outcomes in AMI patients. Two reviewers independently assessed the trials. Differences were resolved by consensus.

Results: Only 2 trials (927 participants) were included. None of the 2 studies showed a significant difference in event rate between the L-arginine and placebo groups. In an overall pooled estimate, there was a 7% reduction in mortality in the L-arginine treatment group (105/459, 22.9%) compared with the control group (111/455, 24.4%), which did not reach statistical significance (risk ratio [RR]: 0.93, 95% confidence interval [CI]: 0.74–1.17; $P = 0.54$).

Conclusion: Oral L-arginine supplementation has no effect on the clinical outcomes of patients with AMI.

Introduction

Cardiovascular disease (CVD) is the biggest burden and dominant chronic disease in many parts of the world, and it has been predicted that CVD will become the main cause of disability and death worldwide in the twenty-first century.[1] Endothelial dysfunction is an early pathophysiological feature and independent predictor of poor prognosis in most forms of cardiovascular disease.[2–3] Normal endothelial functions require an intact L-arginine/nitric oxide (NO) pathway and endothelium. The semi-essential amino acid L-arginine is the only substrate for NO synthesis in vascular endothelial cells, which causes blood vessel relaxation. Therefore, this amino acid has the potential to improve endothelial function and is expected to be used in the treatment of coronary artery disease (CAD) and other vascular disorders.[4] Preliminary evidence suggests that L-arginine may be useful in the treatment of medical conditions that are improved by vasodilation, such as angina, atherosclerosis, CAD, erectile dysfunction, heart failure, and intermittent claudication/peripheral vascular disease.[5–7]

A recent meta-analysis indicates that individuals with apparently impaired endothelial function are likely to benefit from short-term oral L-arginine intake.[8] Patients with acute myocardial infarction (AMI), whose endothelial function is significantly impaired, are most likely to benefit from L-arginine supplementation. Prior studies suggest that administration of L-arginine reduces myocardial infarction size in animal models in vivo and improves myocardial performance in rat hearts in vitro.[9] However, it is still unclear whether L-arginine therapy has any effect on clinical outcomes in patients with AMI.

Previously published trials have suggested that oral L-arginine administration may affect clinical outcomes in AMI individuals. However, the conclusions of these studies were inconsistent. The aim of the present study was to identify, analyze, and combine all published randomized controlled trials that investigated the effects of L-arginine therapy on clinical outcomes of patients with AMI.

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Methods

Literature Search

We systematically searched PubMed (1966–January 2009), Embase (1966-January 2009), the Cochrane Library, previous reviews, and reference lists from identified articles. The search strategy paired the term "arginine" with the following: "coronary heart disease," "myocardial infarction," "cardiovascular disease," "ischemia," and "trial."

Study Selection

We included completed, published, and nonconfounded randomized controlled trials of AMI treatments with the addition of oral L-arginine to standard post infarction therapy, in which participants were randomly assigned to an L-arginine intervention or a control group.

Quality Assessment

We assessed studies for quality of randomization, blinding, reporting of withdrawals, generation of random numbers, and concealment of allocation. Trials scored 1 point for each area addressed, therefore receiving a score between 0 and 5 (highest level of quality).[10]

Data Extraction

All literature searches were independently reviewed by 2 authors (TS, H-mS) to identify relevant trials that met the inclusion criteria. Disparities were resolved by discussion. We extracted data on study sample, population characteristic (age, sex, and baseline comorbidities), interventions (type, dose, and administrated frequency of L-arginine), length of follow-up, and total clinical events. Total clinical events included all-cause mortality, myocardial reinfarction, successful resuscitation, shock/pulmonary edema, recurrent myocardial ischemia, and hospitalization for heart failure, adverse events, missing patient data as a result of withdrawals, non-intention to treat analysis, and loss to follow-up.

Statistical Analysis

Statistical analyses were performed with Stata software (version 9.0; Stata Corporation, College Station, TX) and REVMAN software (version 5.0; Cochrane Collaboration, Oxford, United Kingdom). A fixed effects model was used for data synthesis and analysis.[11] Statistical heterogeneity of treatment effects between studies was formally tested with Cochran's test for heterogeneity ($P < 0.1$). The I^2 statistic was also examined, and we considered $I^2 > 50\%$ to indicate significant heterogeneity between the trials.[12] We calculated risk ratios (RR), with 95% confidence intervals (CI), for dichotomous data.

Results

Search Results

The combined search of PubMed, Embase, the Cochrane Library, and manual approach (searching previous studies cited in previous reviews and reference lists from identified articles) of randomized controlled trials resulted in 1770 articles, of which only 2 eligible randomized controlled studies were identified.

Study Characteristics

We identified 2 trials with 927 subjects for inclusion in our study. The table shows the characteristics of the included trials (Table 1). The sample size of the 2 trials was 153 and 774 subjects, respectively. The average age of patients was 64 and 60 years, respectively. Doses of L-arginine in both studies were 9 g per day, and the treatment duration varied from 30 days to 6 months. L-arginine was administered 3 times a day in both of the studies.

Data Quality

Both of the trials included were randomized, prospective, double-blinded, and placebo-controlled. Both of the studies reported adequate details of withdrawals.

Effects of L-arginine Treatment on Clinical Outcomes of AMI

The event rate varied between trials and none of the 2 trials[13–14] showed a significant difference between the L-arginine and placebo groups. Combining the trials, there was a 7% reduction in mortality in the L-arginine treatment group (105/459, 22.9%) compared with the control group (111/455, 24.4%), which did not reach statistical significance (RR: 0.93, 95% CI: 0.74–1.17; $P = 0.54$; Figure 1). There was no evidence of heterogeneity ($\chi^2 = 1.85$, $I^2 = 46\%$, $P = 0.17$).

Table 1. Characteristics of Populations, Interventions, and Outcomes in Included Trials

Study ID	Year	L-arginine Dose (g/d)	Frequency (times/d)	Study Duration (d)	Participants	No. of Subjects	Mean Age (y)	Study Design
ARAMI[13]	2005	9	3	30	AMI patients	774	64	R, PC, DB
VINTAGE MI[14]	2006	9	3	180	AMI patients	153	60.2 (14.2)	R, PC, DB

Abbreviations: AMI, acute myocardial infarction; DB, double blind; PC, placebo controlled; R, randomized.

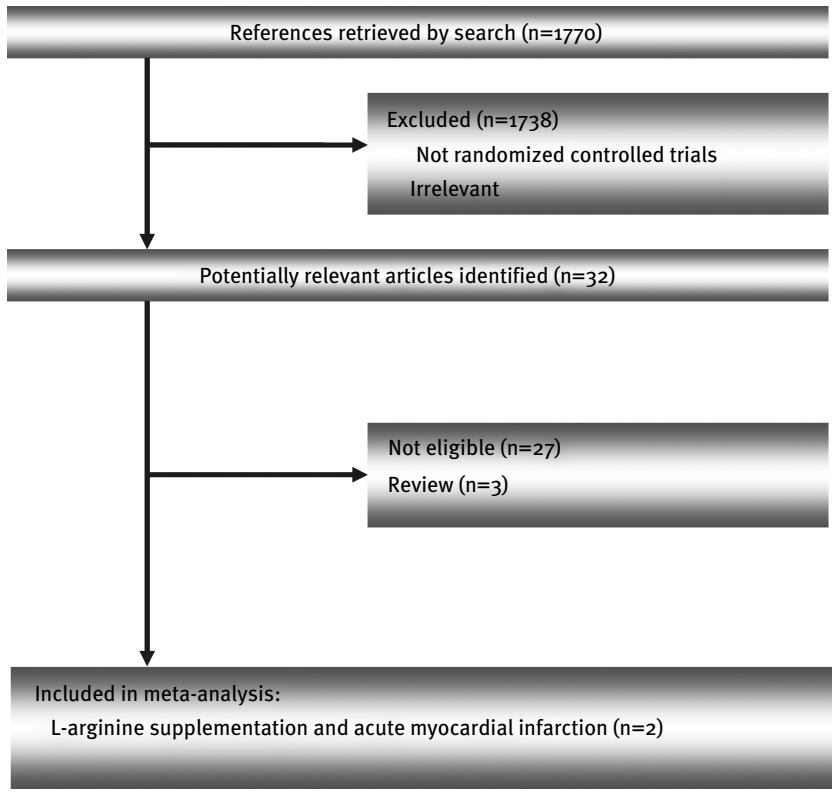

Figure 1. Flow diagram of the trial selection process. Flow chart showing number of citations retrieved by individual searches and number of trials included in review.

Discussion

Our meta-analysis found that L-arginine therapy was not associated with a significant change in the risk of total events in AMI patients. Only 2 randomized controlled trials[13–14] evaluated the association between L-arginine treatment and clinical outcomes of unstable CAD patients. The results of the ARAMI pilot trial[13] suggest that the supplementation with L-arginine seems to improve the clinical course of AMI. However, the VINTAGE MI study[14] finds that L-arginine is associated with higher total event rates and postinfarction mortality than a placebo. Results of both studies do not reach statistical significance.

Although we identified no heterogeneity in the results of the analyses of effect on outcome, the small number of participating trials with substantial numbers of these end points meant that statistical power to detect such differences was suboptimal. Characters of patients, initial time of L-arginine treatment, the difference of combined medical treatment (which included percutaneous coronary intervention [PCI], β-blockers, statins, angiotensin-converting

Figure 2. Fixed effects meta-analysis of relative risk (95% CI) of clinical events with L-arginine treatment compared with placebo in acute myocardial infarction patients. Sizes of data markers indicate the weight of each study in the analysis. Abbreviations: CI, confidence interval; df, degree of freedom.

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enzyme inhibitors, etc) may have influenced the results of these studies. The first dose of L-arginine was administrated to patients within 24 to 48 hours after they presented with symptoms of AMI in the ARAMI trials. However, in the VINTAGE MI study, patients were enrolled within 3 to 21 days after the onset of AMI, and then after a mean of 5.9 days of baseline evaluation, the first dose of L-arginine was given about 1 to 4 weeks after they presented with symptoms of AMI. This significant difference may be an important reason for the heterogeneous outcome between the 2 studies. Interestingly, there is another very significant difference between the 2 trials: none of the patients in the ARAMI trials received PCI treatment and most of the participants in the VINTAGE MI study were treated by acute PCI (percutaneous coronary intervention). Perfect medical treatment following MI could have masked the potential benefit of L-arginine in the VINTAGE MI study.

Although oral L-arginine supplement seems a plausible and attractive strategy for reversing endothelial dysfunction in stable CAD patients, studies of L-arginine in patients with AMI have shown mixed results. There are several potential mechanisms by which L-arginine supplementation, which is an effective therapy to improve endothelial function, may be useless in postmyocardial infarction patients. Firstly, supplementation of L-arginine may increase iNOS (induced NOS nitric oxide synthase) activity in patients with AMI, which may account for the negative effect of L-arginine observed during the postinfarction period. Second, the effect of the underlying medical inventions (such as statins, angiotensin-converting enzyme inhibitors, β-blockers, etc) following AMI could have masked the potential benefit of L-arginine.

One important limitation of our meta-analysis was that only 2 trials have been combined for the analysis of AMI outcomes, 1 of which was over 5 times the size of the other. Clearly when there are only 2 such trials, the results would be overwhelmed by the larger one. Research efforts should now be concentrated on higher quality, more rigorous randomized trials. Studies are needed that are powered to detect important effects on clinical outcomes of patients with unstable CAD and other cardiovascular diseases, to resolve the uncertainty about the clinical effectiveness and safety of this type of intervention.

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