L-Arginine Therapy in Acute Myocardial Infarction
The Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) Randomized Clinical Trial

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The amino acid L-arginine, the substrate for nitric oxide synthase (NOS), is widely available and publicized as having benefits for patients with hypertension, angina, heart failure, and sexual dysfunction. It is estimated that 40% of US residents take some type of dietary supplement. A recent statement from the Institute of Medicine called for applying the same principles and standards of evidence of treatment effectiveness and safety to all therapies, whether currently labeled as conventional medicine or complementary and alternative medicine.

Context  The amino acid L-arginine is a substrate for nitric oxide synthase and is increasingly used as a health supplement. Prior studies suggest that L-arginine has the potential to reduce vascular stiffness.

Objective  To determine whether the addition of L-arginine to standard postinfarction therapy reduces vascular stiffness and improves ejection fraction over 6-month follow-up in patients following acute ST-segment elevation myocardial infarction.


Patients  A total of 153 patients following a first ST-segment elevation myocardial infarction were enrolled; 77 patients were 60 years or older.

Intervention  Patients were randomly assigned to receive L-arginine (goal dose of 3 g 3 times a day) or matching placebo for 6 months.

Main Outcome Measures  Change in gated blood pool–derived ejection fraction over 6 months in patients 60 years or older randomized to receive L-arginine compared with those assigned to receive placebo. Secondary outcomes included change in ejection fraction in all patients enrolled, change in noninvasive measures of vascular stiffness, and clinical events.

Results  Baseline characteristics, vascular stiffness measurements, and left ventricular function were similar between participants randomized to receive placebo or L-arginine. The mean (SD) age was 60 (13.6) years; of the participants, 104 (68%) were men. There was no significant change from baseline to 6 months in the vascular stiffness measurements or left ventricular ejection fraction in either of the 2 groups, including those 60 years or older and the entire study group. However, 6 participants (8.6%) in the L-arginine group died during the 6-month study period vs none in the placebo group \( (P = .01) \). Because of the safety concerns, the data and safety monitoring committee closed enrollment.

Conclusions  L-Arginine, when added to standard postinfarction therapies, does not improve vascular stiffness measurements or ejection fraction and may be associated with higher postinfarction mortality. L-Arginine should not be recommended following acute myocardial infarction.

Clinical Trial Registration  ClinicalTrials.gov, NCT00051376

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a hallmark of aging.4-7 The age-associated increase in arterial stiffness is attributed not only to structural changes in the arterial wall8 but also to an age-associated decline in endothelial function.9-11 The administration of L-arginine improves endothelial function in healthy elderly individuals and patients with vascular disease,10,12 in addition to improving noninvasive measures of vascular stiffness.13

The Vascular Interaction with Age in Myocardial Infarction (VINTAGE MI) clinical trial was designed to test whether the addition of L-arginine to standard postinfarction therapy in patients following a first STEMI over a 6-month period would decrease vascular stiffness and improve left ventricular function. Secondary outcomes included clinical events.

METHODS
Patients
The VINTAGE MI study enrolled patients at least 30 years of age within 3 to 21 days of a first STEMI. Cardiac catheterization was performed for clinical reasons. Patients with prior documented Q-wave MI, present cardiogenic shock, active acute coronary syndrome, severe underlying noncardiac disease limiting predicted life span to less than a year, poorly controlled diabetes mellitus, or significant renal (creatinine >3.0 mg/dL [265.2 µmol/L]) or hepatic disease were excluded. The study was approved by the institutional review board at the Johns Hopkins Medical Institutions, and all participants gave informed written consent.

In addition to standard demographic variables, peak creatine phosphokinase, and troponin I values were collected, as well as the number of leads on the admission electrocardiogram (ECG) with at least 1 mm ST-segment elevation, the sum of ST-segment deviation, and medical therapies administered. Catheterization variables assessed included initial and final Thrombolysis in Myocardial Infarction (TIMI) flow grade in the infarct vessel, whether a percutaneous coronary intervention was performed, the number of vessels with a 70% or greater stenosis, and the Duke Coronary Artery Disease score.14

Baseline Study Evaluation
Evaluation of left ventricular function and vascular stiffness were performed at a mean of 5.9 days (median, 4; 25th percentile, 3; 75th percentile, 8; range, 3-21 days) following admission for acute myocardial infarction. These included:

1. Gated blood pool scan: Supine and upright resting gated blood pool scans were obtained after in vivo labeling of red blood cells with 25 to 30 mCi of technetium 99m as previously described.15 All scans were read by one of the investigators (L.C.B.), who was blinded to treatment assignment, patient age, identity, and time of study. Global left ventricular ejection fraction was calculated from time activity curves generated from left ventricular regions of interest. Infarct zone and remote zone ejection fraction and absolute cardiac volumes were determined as previously described.15

2. Pulse pressure: Pulse pressure was calculated as the difference between sitting systolic and diastolic blood pressures measured at the time of the gated blood pool scan. The average of 3 measurements by cuff sphygmomanometry was used.

3. Arterial compliance: Arterial compliance was measured with an automated tonometry device that was positioned over the radial artery (CR-2000, Hypertension Diagnostics Inc), which has been validated with invasive studies.16 The tonometer was calibrated with sphygmanometric blood pressures. Steady state 30-second pressure recordings were recorded and digitized for each patient. Steady state aortic pressure waves were reconstructed using transfer functions. Total arterial compliance was calculated using the area under the diastolic portion of the pressure decay curve, a method also previously validated.17

4. Pulse wave velocity: Flow waves were recorded from the right common carotid and right femoral arteries using pulse wave Doppler flow probes (model HP5500, Phillips Inc, Andover, Mass). Measurements were made with participants in the supine position after a 15-minute equilibration period. The pulse wave velocity was determined by the quotient of a distance and a time measure with simultaneous ECG recordings as previously described.18

5. Arterial elastance: Arterial elastance was calculated from the noninvasive estimation of end systolic pressure and stroke volume from the gated blood pool scan. End systolic pressure was estimated by 0.9 × arterial systolic pressure.19

Treatment
Once baseline data were obtained, all patients were randomized in a double-blind fashion to study drug, consisting of L-arginine (MK Health Food Distributor, Nature’s Life, Larkspur, Calif) or matching placebo. High-performance liquid chromatography of separate lots of active study drug revealed between a 509- and 516-mg L-arginine capsule. Stratification was made by age (<60 years and ≥60 years) and sex. Within any age group, stratification was also made by pulse pressure (<50 mm Hg or ≥50 mm Hg).

Block sizes were randomly selected among sizes 2, 4, and 6 within each stratum.

Participants started the study drug, 1 g three times daily for 1 week, increasing to 2 g three times daily in week 2, followed by 3 g three times daily in week 3. Patients were maintained at this dose for 6 months. If adverse effects occurred during dose titration, the dose was lowered to the prior dose that was tolerated. All patients were followed up in our study clinic at 1 month, 3 months, and 6 months. In all patients, capsule counts for adherence were determined at each visit.

Assessment by an investigator at each visit was also made for new clinical heart failure and new ischemic events. A blinded clinical events committee adjudicated admissions for heart failure,
new myocardial infarction, and death from the medical record. At each visit, the investigator also assessed the occurrence of any adverse events and medication adverse effects. After 6 months of follow-up, repeat vascular and ventricular function testing were performed. At baseline and at 6 months, plasma L-arginine levels were measured by high-performance liquid chromatography, as previously described.20

**Statistical Analysis**

Baseline comparability of demographic and other covariates between the treatment groups was checked. For treatment comparisons, a 2-tailed P value of <.05 was considered significant in the primary analysis, and in secondary analyses a P value of <.01 was considered significant. For the primary analysis, a composite ranking based on 6-month mortality and change in ejection fraction between baseline and the 6-month visit was used.21,22 Patients who died prior to the 6-month follow-up were ranked on their time to death and were ranked worse than all survivors. Patients surviving 6 months were ranked by the difference between their ejection fractions at baseline and 6 months with those exhibiting the most deterioration in ejection fraction ranked worst. The Wilcoxon rank test was used to compare the placebo and L-arginine groups. The primary end point analysis involved those patients randomized (analysis by intention to treat) who were 60 years or older. Event rates for the combined and individual clinical outcomes of death, hospital admission for heart failure, and hospitalization for myocardial infarction were estimated using the Kaplan-Meier life-table method and compared by the log-rank statistic.

Means of pulse pressure, arterial compliance, pulse-wave velocity, arterial elastance, ejection fraction, and cardiac volumes at baseline and 6 months within the placebo and L-arginine groups were determined. Baseline and 6-month variables between the 2 treatment groups were compared using the unpaired t test. Data are expressed as the mean and standard deviation.

We planned to enroll 180 patients aged 60 years or older, which allowed for nonadherence and dropout as high as 20%, and mortality as high as 10%, to obtain power of about 0.90 to detect an absolute difference in 6-month change in ejection fraction of 6% between the 2 groups. We also planned to enroll 100 patients from ages 30 to 59 years with an estimated dropout as high as 10% to detect any association of baseline arterial stiffness and age with a power of 0.90. The study planned for data and safety monitoring reports compiled every 6 months during patient enrollment. The data and safety monitoring committee recommended stopping patient enrollment at 2.5 years after the start of recruitment due to excess mortality in patients in the L-arginine group. All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, NC).

**RESULTS**

**Patient Characteristics**

One hundred fifty-three patients with a first STEMI and meeting all entry criteria were enrolled from February 2002 through June 2004 (Figure). Patient characteristics according to randomization assignment are presented in Table 1. Seventy-seven patients were 60 years or older, and 89 patients had baseline pulse pressure of 50 mm Hg or higher. The majority of patients had percutaneous coronary intervention of the infarct vessel with restoration of TIMI 3 flow. The number of patients with single-, double-, and triple-vessel coronary disease, as well as the infarct site and the coronary artery disease prognostic score, were similar between the 2 groups. Estimates of infarct size by cardiac enzymes and ECG were also similar between the 2 groups. At the time of randomization (mean 5.9 days from admission; median, 4; 25th percentile, 3; 75th percentile, 8; range, 3-21 days), the majority of patients were treated with standard postinfarct therapies.

**Baseline Vascular and Ventricular Function**

Baseline vascular properties measured on standard postinfarct therapies are presented in Table 2. There were no baseline differences between measurements of vascular stiffness in the 2 study groups, including pulse pressure, arterial elastance, pulse wave velocity, and radial artery compliance. Gated blood pool scan measures of left ventricular function, including global and regional ejection fraction and cardiac volumes, were also similar (Table 2).

**Response to Study Drug**

Interim analyses for safety end points were performed every 6 months, and the data and safety monitoring committee terminated the study early for safety concerns. Six-month studies were obtained in 55 participants in the L-arginine group and 59 in the placebo group (Figure). By capsule counts, the percentage of patients adherent with the study drug at 1, 3, and 6 months ranged from 80% to 90% in both L-arginine and placebo groups. Two thirds of patients at the 6-month fol-
low-up were taking l-arginine or matching placebo at the goal dose of 3 g three times a day. L-Arginine plasma concentrations are shown in Table 3. Baseline l-arginine levels were within the normal range (60-100 µmol/L) in both groups. Following 6 months of therapy, levels went up slightly in both randomized groups, with no difference between plasma l-arginine concentrations in patients in either group. Neither the change in l-arginine levels from baseline to 6 months nor stratification by the amount of l-arginine taken at the 6-month visit showed any effect of study drug on l-arginine concentrations.

l-Arginine therapy was generally well tolerated. As shown in Table 4 adverse effects were generally minor and equally common among patients in both groups.

Six-month vascular property values are presented in Table 2. Arterial elastance, arterial compliance, pulse pressure, and pulse wave velocity were similar between placebo and l-arginine treated patients. The 6-month vascular stiffness values in patients 60 years or older and patients with a baseline pulse pressure 50 mm Hg or higher were also similar between patients in either group.

The primary outcomes (6-month median change in ejection fraction, with death as the worst response, in patients 60 years and older) were −1.0% in the l-arginine group and −1.0% in the placebo group (P = .89 by Wilcoxon test). The median change in ejection fraction from baseline to 6 months with deaths counted as the worst outcome in the entire population was 0.0% in the l-arginine group and −1.0% in patients in the placebo group (P = .89 by Wilcoxon test). There were no ejection fraction differences between l-arginine and placebo in patients who had baseline pulse pressures of at least 50 mm Hg.

Changes in cardiac volumes and ejection fraction in patients with paired baseline and 6-month studies are also presented in Table 2. Cardiac volumes and ejection fraction at 6 months were similar between patients in both groups. Additionally, 6-month noninfarct and infarct zone ejection fraction were not different in the 2 groups. In patients 60 years or older, l-arginine therapy had no impact on left ventricular volumes or ejection fraction.

Six-month clinical events, including death, myocardial infarction, and hospitalization for heart failure, occurred in 12 (16.7%) patients in the l-arginine group compared with 7 (10.1%) patients in the placebo group. Death occurred in 6 patients (8.6%) in the l-arginine group and none in the placebo group.

### Table 1. Baseline Characteristics According to Randomized Assignment

<table>
<thead>
<tr>
<th>Risk factors, No. (%)</th>
<th>L-Arginine (n = 78)</th>
<th>Placebo (n = 75)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>60.2 (14.2)</td>
<td>60.4 (12.9)</td>
<td>.92</td>
</tr>
<tr>
<td>Age ≥60 y, No. (%)</td>
<td>39 (50)</td>
<td>38 (51)</td>
<td>.93</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>53 (68)</td>
<td>51 (68)</td>
<td>.99</td>
</tr>
<tr>
<td>Killip class I</td>
<td>48 (62)</td>
<td>51 (70)</td>
<td>.28</td>
</tr>
<tr>
<td>Pulse pressure ≥50 mm Hg</td>
<td>46 (59)</td>
<td>43 (57)</td>
<td>.84</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (22)</td>
<td>13 (17)</td>
<td>.46</td>
</tr>
<tr>
<td>Current smoker</td>
<td>29 (38)</td>
<td>32 (43)</td>
<td>.53</td>
</tr>
<tr>
<td>Infarct vessel–LAD</td>
<td>37 (47)</td>
<td>33 (44)</td>
<td>.67</td>
</tr>
<tr>
<td>Single-vascular disease</td>
<td>29 (37)</td>
<td>23 (31)</td>
<td>.40</td>
</tr>
<tr>
<td>Initial TIMI flow 0, 1</td>
<td>47 (60)</td>
<td>45 (60)</td>
<td>.97</td>
</tr>
<tr>
<td>Final TIMI flow 3</td>
<td>57 (83)</td>
<td>54 (82)</td>
<td>.90</td>
</tr>
<tr>
<td>Fibrinolytic therapy given</td>
<td>15 (19)</td>
<td>19 (25)</td>
<td>.36</td>
</tr>
<tr>
<td>PCI of infarct vessel</td>
<td>69 (89)</td>
<td>66 (88)</td>
<td>.93</td>
</tr>
<tr>
<td>Coronary artery disease score, mean (SD)</td>
<td>48.4 (15.7)</td>
<td>49.1 (15.3)</td>
<td>.78</td>
</tr>
<tr>
<td>Peak CPK, mean (SD), IU/L</td>
<td>2314.4 (2311.8)</td>
<td>2210.8 (2175.8)</td>
<td>.78</td>
</tr>
<tr>
<td>Troponin I, mean (SD), ng/mL</td>
<td>79.0 (156.9)</td>
<td>79.4 (112.2)</td>
<td>.99</td>
</tr>
<tr>
<td>ECG leads with 1 mm ST-segment elevation, mean (SD)</td>
<td>4.3 (2.3)</td>
<td>4.4 (2.5)</td>
<td>.92</td>
</tr>
<tr>
<td>Sum of ST-segment deviation, mean (SD), mm</td>
<td>13.0 (12.3)</td>
<td>12.6 (11.8)</td>
<td>.84</td>
</tr>
<tr>
<td>Medication at study entry, No. (%)</td>
<td>78 (100)</td>
<td>75 (100)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Aspirin</td>
<td>71 (91)</td>
<td>68 (88)</td>
<td>.54</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>71 (91)</td>
<td>68 (88)</td>
<td>.54</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>71 (91)</td>
<td>68 (88)</td>
<td>.85</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>71 (91)</td>
<td>73 (97)</td>
<td>.10</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitor</td>
<td>75 (96)</td>
<td>73 (97)</td>
<td>.68</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACE, angiotensin-converting enzyme; CPK, creatine phosphokinase; ECG, electrocardiogram; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LAD, left anterior descending; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

### Table 2. Vascular and Ventricular Properties at Baseline and 6 Months*

<table>
<thead>
<tr>
<th>Vascular and Ventricular Properties</th>
<th>L-Arginine, Mean (SD)</th>
<th>Placebo, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>6 Months</strong></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>52.6 (13.3)</td>
<td>51.6 (12.7)</td>
</tr>
<tr>
<td>Arterial elastance, mm Hg/mL</td>
<td>1.6 (0.4)</td>
<td>1.5 (0.4)</td>
</tr>
<tr>
<td>Pulse-wave velocity, cm/s</td>
<td>807.4 (261)</td>
<td>777.0 (271)</td>
</tr>
<tr>
<td>Radial artery compliance, mL/mm Hg</td>
<td>1.7 (0.6)</td>
<td>2.0 (0.9)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>54.9 (10.8)</td>
<td>55.7 (12.5)</td>
</tr>
<tr>
<td>Infarct zone ejection fraction, %</td>
<td>37.7 (15.3)</td>
<td>35.9 (14.0)</td>
</tr>
<tr>
<td>Noninfarct zone ejection fraction, %</td>
<td>84.1 (14.9)</td>
<td>84.8 (12.7)</td>
</tr>
<tr>
<td>End diastolic volume index, mL/m²</td>
<td>79.9 (17.3)</td>
<td>85.9 (23.0)</td>
</tr>
<tr>
<td>End systolic volume index, mL/m²</td>
<td>36.7 (16.6)</td>
<td>39.9 (22.8)</td>
</tr>
</tbody>
</table>

*There were no baseline or 6-month differences between the 2 groups.

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placebo group (P = .01). Five of the patients who died were 60 years or older (15.5%, P = .02 compared with placebo in this age group). The 5 deaths included a patient dying of myocardial rupture following a recurrent anterior infarction, 2 patients were found dead at home without prior symptoms, and 2 patients died of presumed sepsis. After termination of the study treatments, a sixth patient in the L-arginine group died. The patient died suddenly 4 months following his acute anterior myocardial infarction and 3 weeks following cessation of study drug.

**COMMENT**

The VINTAGE MI study demonstrated that 6 months of L-arginine added to standard postinfarct medications did not reduce noninvasive measures of vascular stiffness, improve ejection fraction, or improve clinical outcomes. To the contrary, we noted a possible increased risk of death in older patients after infarction while taking L-arginine compared with those taking a placebo, leading to the early termination of the study. These findings have broad public health implications given the increasing availability and use of L-arginine in patients with and without established cardiovascular diseases. Advanced age is a powerful independent predictor of short-term morbidity and mortality in postinfarction patients.24-26 This increased risk may be due in part to the age-associated changes in the cardiovascular system, which alter the substrate upon which the infarct occurs. One such age-associated change is an increase in vascular stiffness, which increases left ventricular afterload.4,6 The increase in vascular load is likely causally related to an age-related increase in left ventricular wall thickness, a decrease in exercise reserve, and an increased risk of cardiovascular morbidity and mortality in healthy men and women.6,7,37 In patients with left ventricular dysfunction, increased vascular load relative to ventricular contractility results in depression of myocardial efficiency.20,29 Following a myocardial infarction, increased load contributes to left ventricular dilatation and ultimately, poor prognosis.30,31 The attenuation of left ventricular remodeling by angiotensin-converting enzyme inhibitors, partly by reducing vascular load, reduces morbidity and mortality.32

Endothelial dysfunction is another age-associated change that may impact prognosis in older patients following myocardial infarction. It is common in seemingly healthy elderly subjects,9 as well as in patients with coronary artery disease.33 Since endothelial dysfunction affects conduit as well as arteriolar vessels, it likely contributes to the age- and disease-associated increases in peripheral vascular resistance, arterial stiffness, and vascular load.31,34,35 The mechanisms for endothelial dysfunction are likely multifactorial16,38 although the result is a loss of available nitric oxide.

One mechanism to increase nitric oxide synthesis by vascular endothelium is to provide more substrate for the endothelial-specific isoform of nitric oxide synthase (eNOS).30 L-Arginine is an important substrate for this enzyme.39 Although the availability of intracellular L-arginine for eNOS does not appear rate limiting,40 coronary and brachial endothelial function improves12,41,42 in addition to improved measurements of arterial compliance following supplemental L-arginine administration in doses similar to those used in this trial.13

The VINTAGE MI study is the largest prospective study of L-arginine in patients with coronary artery disease and the first, to our knowledge, testing whether L-arginine administration in a postinfarct population improves measures of vascular stiffness and left ventricular remodeling following a first STEMI. In this study, 6 months of L-arginine therapy failed to decrease several vascular stiffness measurements. This lack of effect was also evident in prespecified subgroups with elevated baseline vascular stiffness,

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**Table 3. Plasma Concentrations of L-Arginine at Baseline and Six Months**

<table>
<thead>
<tr>
<th>L-Arginine (n = 56)</th>
<th>Placebo (n = 55)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Arginine plasma concentration, mean (SD), µmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>90.2 (7.3)</td>
<td>86.5 (0.7)</td>
</tr>
<tr>
<td>Six month</td>
<td>94.8 (6.2)</td>
<td>93.0 (7.6)</td>
</tr>
<tr>
<td>Difference</td>
<td>4.6 (5.4)</td>
<td>6.5 (6.3)</td>
</tr>
</tbody>
</table>

| Dose effect at 6 mo, L-arginine patients only, µmol/L | | |
| Plasma concentration | 95.6 (5.7) | 96.8 | 96.5 (4.9) | 94.1 (6.7) |
| Change from baseline | 7.1 (7.1) | 3.0 | 2.2 (4.2) | 4.1 (4.8) |

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**Table 4. Adverse Effects**

<table>
<thead>
<tr>
<th>No. (%) of Adverse Effects</th>
<th>L-Arginine (n = 77)</th>
<th>Placebo (n = 75)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse effect</td>
<td>33 (43)</td>
<td>27 (36)</td>
<td>.39</td>
</tr>
<tr>
<td>Bloating</td>
<td>9 (12)</td>
<td>8 (11)</td>
<td>.84</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (8)</td>
<td>7 (9)</td>
<td>.73</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (7)</td>
<td>7 (9)</td>
<td>.52</td>
</tr>
<tr>
<td>Flushing</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>.99</td>
</tr>
<tr>
<td>Other*</td>
<td>19 (25)</td>
<td>11 (15)</td>
<td>.12</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

*Other includes belching, constipation, flatus, and indigestion.
including patients at least 60 years of age and those with baseline pulse pressure higher than 50 mm Hg.

Plasma L-arginine levels were normal at baseline, and increased similarly following 6 months of therapy with L-arginine and placebo. Although plasma levels convey little about intracellular effects, the lack of any change in vascular or ventricular measurements between L-arginine and placebo treated patients suggests that any decrease in vascular stiffness by L-arginine may be possible only in patients with preexisting L-arginine deficiency.43 The adaptive change in L-arginine catabolism by hepatic arginase activity with increased dietary intake of L-arginine likely explains the small changes in L-arginine concentration in our patients following 6 months of therapy.44,45 Furthermore, the potential benefits of supplemental L-arginine on enhancing nitric oxide production may be inhibited by the age-associated increases in arginase levels and endogenous NOS inhibitors.37,46 Our findings are consistent with those of Blum and coworkers,47 who reported that the addition of L-arginine (9 g daily) to standard anti-ischemic therapy had no effect on nitrogen oxides, serum adhesion molecules, or flow-mediated brachial artery dilation in 30 patients with stable coronary disease.

There are several potential mechanisms by which L-arginine therapy may be harmful in post–myocardial infarction patients. In the setting of NOS cofactor tetrahydrobiopterin deficiency, instead of generating nitric oxide, ENOS becomes a source of reactive oxygen species generation that could be enhanced with L-arginine supplementation.48 In an animal model of pressure overload, tetrahydrobiopterin levels were reduced resulting in marked generation of reactive oxygen species, metalloprotease production, fetal gene expression, and left ventricular dilatation.49 All these adverse cardiac responses to pressure overload were ameliorated in eNOS knock-out mice or by providing dietary tetrahydrobiopterin. L-Arginine supplementation also leads to an increase in homocysteine production, which can result in worsening, not improvement, of endothelial function and atherosclerosis.50 Furthermore, in the setting of atherosclerotic disease, the inducible isof orm of nitric oxide synthase (iNOS) is expressed, resulting in production of peroxynitrite and consumption of nitric oxide, potentially worsening atherosclerosis.38,48,50 Whereas decreased availability of L-arginine inhibits iNOS protein expression, increased cellular uptake of L-arginine results in increased iNOS protein expression and enzyme activity.37 High levels of iNOS, nitric oxide, and peroxynitrite contribute to the myocardial dysfunction and systemic vasodilatation that occur in both septic and cardiogenic shock.52 These potential consequences of L-arginine supplementation may explain, in part, the worse clinical outcomes in the older patients in this study randomized to L-arginine. It is important to note that trials are currently under way testing the hypothesis that inhibition of NOS may be beneficial after myocardial infarction (see http://www.clinicaltrials.gov, NCT00112281); the current findings are consistent with the thesis of these trials.

A potential reason for the failure of L-arginine to reduce vascular stiffness measurements was that L-arginine levels were normal to begin with. The lack of any dose response in plasma L-arginine levels from 0 to 9 g suggests that higher doses of L-arginine would not have resulted in any biological effect in this population. Additionally, a large majority of patients were already taking medications that improve vascular function, including angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.53,54 The lack of change in ejection fraction over 6 months and lack of remodeling may be related to the large proportion of patients receiving early percutaneous coronary intervention with establishment of coronary patency.

This study has several limitations. Due to the early termination of VINTAGE MI, we enrolled about half of the planned study population. Nevertheless, the small change in ejection fraction observed among the 153 enrolled patients makes it unlikely that a benefit of L-arginine on ejection fraction following STEMI would have been found, even if the entire planned population were enrolled. Post hoc power calculations to detect a 6-unit difference between L-arginine and placebo assigned groups in change in ejection fraction from baseline to 6-month follow-up based on the enrolled population was 0.71 for participants 60 years and older and 0.94 for the entire study population. Mortality was not an a priori primary end point. The excess mortality was an unexpected safety monitoring concern and the results could be due to (small but nonzero) chance. Nevertheless, we concurred with the data and safety monitoring committee’s independent recommendation for early termination of treatment with L-arginine.

In conclusion, L-arginine therapy should not be given to patients following a myocardial infarction. It neither alters noninvasive measures of vascular stiffness nor improves left ventricular function. L-Arginine therapy in older patients with diffuse atherosclerosis may worsen clinical outcomes.

Author Contributions: Drs Schulman and Gerstenblith had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Schulman, Becker, Champion, Terrin, Forman, Capriotti, Hare, Gerstenblith.

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Obtained funding: Schulman, Kass, Gerstenblith.

Administrative, technical, or material support: Schulman, Kass, Champion, Terrin, Ernst, Kelemen, Townsend, Capriotti, Hare, Gerstenblith.

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Financial disclosures: None reported

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Funding/Support: The study was supported by Na-
tional Heart, Lung, and Blood Institute grant HL70059.

Role of the Sponsor: The funding agency had no role in
development or completion of the study, in the collec-
tion, analysis, and interpretation of the data, or in the
preparation, review, or approval of the manuscript.

Acknowledgment: We thank the members of the data
and safety monitoring committee and the clinical events
committee for their commitment to the trial.

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