

diac enzyme criteria occurred in patients who received thrombolytic therapy within 1 hour of symptom onset; that rate decreased with time, to 10% at 3 hours.

The trouble is, a mere 3% of ASSENT-3 participants were treated within 1 hour of MI symptom onset; 27% received thrombolytics within 2 hours. Getting more patients to come to the hospital or call an ambulance early after symptom onset has proved a daunting task. "So far every campaign to do that both here and abroad has failed," Dr. Gersh noted.

Transfer mania—the urge to transport everyone with an acute MI for primary PCI—is driven by half a dozen studies

showing lower rates of death, stroke, and recurrent MI, he said. However, many of these trials were conducted in small European countries where transfer times are so short that the applicability of the results to U.S. patients becomes questionable.

This point was driven home by a recent report from the U.S. National Registry of Myocardial Infarction investigators (Circulation 2005;111:761-7). In analyzing nearly 4,300 MI patients transferred from one hospital to another for primary PCI during 1999-2002, they found only 4.2% had a less than 90-minute interval between time of arrival at the initial hospital to balloon inflation at the PCI center, as is recom-

mended by current American College of Cardiology/American Heart Association guidelines for the use of primary PCI.

The Mayo Clinic has two helicopters and a fixed-wing airplane for transfer of MI patients from outlying hospitals. Here's what Mayo cardiologists recommend to physicians at community hospitals in their region without primary PCI capability: If a patient's duration of symptoms is less than 120 minutes, give full-dose thrombolytics and then transfer so the patient can undergo either routine elective angiography or, in the event of persistent ischemia, rescue PCI, Dr. Gersh said. Beyond 2 hours, Dr. Gersh and his col-

leagues suggest direct transfer for primary PCI without preceding thrombolytics. This is a situation where facilitated PCI—that is, giving lytics and/or platelet glycoprotein IIb/IIIa inhibitors locally followed by transfer for PCI to maximize vessel opening—is very attractive. The results of ongoing trials of this approach are eagerly awaited, Dr. Gersh said.

If facilitated PCI proves effective, it will be particularly advantageous when transfer delays occur. For instance, last year the Mayo Clinic's air transport service was grounded by severe weather for some part of 58 days. "That's a fact of life in many parts of the United States," he noted. ■

## **INTEGRILIN® (eptifibatide) INJECTION** **For Intravenous Administration**

### **BRIEF SUMMARY (For full Prescribing Information, see package insert.)**

#### **INDICATIONS AND USAGE**

INTEGRILIN is indicated:

- For the treatment of patients with acute coronary syndrome (unstable angina/non-ST-segment elevation myocardial infarction), including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI). In this setting, INTEGRILIN has been shown to decrease the rate of a combined endpoint of death or new myocardial infarction.
- For the treatment of patients undergoing PCI, including those undergoing intracoronary stenting. In this setting, INTEGRILIN has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction, or need for urgent intervention.

In the IMPACT II, PURSUIT and ESPRIT studies of eptifibatide, most patients received heparin and aspirin, as described in CLINICAL TRIALS.

#### **CONTRAINDICATIONS**

Treatment with eptifibatide is contraindicated in patients with:

- A history of bleeding diathesis, or evidence of active abnormal bleeding within the previous 30 days.
- Severe hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg) not adequately controlled on antihypertensive therapy.
- Major surgery within the preceding 6 weeks.
- History of stroke within 30 days or any history of hemorrhagic stroke.
- Current or planned administration of another parenteral GP IIb/IIIa inhibitor.
- Dependency on renal dialysis.
- Known hypersensitivity to any component of the product.

#### **WARNINGS**

**Bleeding.** Bleeding is the most common complication encountered during eptifibatide therapy. Administration of eptifibatide is associated with an increase in major and minor bleeding, as classified by the criteria of the Thrombolysis in Myocardial Infarction Study group (TIMI), (see ADVERSE REACTIONS). Most major bleeding associated with eptifibatide has been at the arterial access site for cardiac catheterization or from the gastrointestinal or genitourinary tract.

In patients undergoing percutaneous coronary interventions, patients receiving eptifibatide experience an increased incidence of major bleeding compared to those receiving placebo without a significant increase in transfusion requirement. Special care should be employed to minimize the risk of bleeding among these patients (see PRECAUTIONS). If bleeding cannot be controlled with pressure, infusion of eptifibatide and concomitant heparin should be stopped immediately.

**Renal Insufficiency.** Approximately 50% of eptifibatide is cleared by the kidney in patients with normal renal function. Total drug clearance is decreased by approximately 50% and steady-state plasma eptifibatide concentrations are doubled in patients with an estimated creatinine clearance <50 mL/min (using the Cockcroft-Gault equation). Therefore, the infusion dose should be reduced to 1 mg/kg/min in such patients (see DOSAGE AND ADMINISTRATION section). There has been no clinical experience in patients dependent on dialysis.

**Platelet Count <100,000/mm<sup>3</sup>.** Because it is an inhibitor of platelet aggregation, caution should be exercised when administering eptifibatide to patients with a platelet count <100,000/mm<sup>3</sup>; there has been no clinical experience with eptifibatide initiated in patients with a platelet count <100,000/mm<sup>3</sup>.

#### **PRECAUTIONS**

##### **Bleeding Precautions**

**Care of the Femoral Artery Access Site in Patients Undergoing Percutaneous Coronary Intervention (PCI).** In patients undergoing PCI, treatment with eptifibatide is associated with an increase in major and minor bleeding at the site of arterial sheath placement. After PCI, eptifibatide infusion should be continued until hospital discharge or up to 18-24 hours, whichever comes first. Heparin use is discouraged after the PCI procedure. Early sheath removal is encouraged while eptifibatide is being infused. Prior to removing the sheath, it is recommended that heparin be discontinued for 3-4 hours and an aPTT of <45 seconds or ACT <150 seconds be achieved. In any case, both heparin and eptifibatide should be discontinued and sheath hemostasis should be achieved at least 2-4 hours before hospital discharge.

**Use of Thrombolytics, Anticoagulants, and Other Antiplatelet Agents.** In the IMPACT II, PURSUIT and ESPRIT studies, eptifibatide was used concomitantly with unfractionated heparin and aspirin (see CLINICAL STUDIES). In the ESPRIT study, clopidogrel or ticlopidine were used routinely starting the day of PCI. Because eptifibatide inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis, including **thrombolytics, oral anticoagulants, non-steroidal anti-inflammatory drugs, and dipyridamole.** To avoid potentially additive pharmacologic effects, concomitant treatment with **other inhibitors of platelet receptor GP IIb/IIIa** should be avoided.

There is only a small experience with concomitant use of eptifibatide and **thrombolytics.** In a study of 180 patients with acute myocardial infarction (AMI), eptifibatide (in regimens up to a bolus of 180 µg/kg followed by a continuous infusion of 0.75 µg/kg/min for 24 hours) was administered concomitantly with the approved "accelerated" regimen of alteplase, a thrombolytic agent. The studied regimens of eptifibatide did not increase the incidence of major bleeding or transfusion compared to the incidence seen when alteplase was given alone.

In the IMPACT II study, 15 patients received a thrombolytic agent in conjunction with the 135/0.5 dosing regimen, 2 of whom experienced a major bleed. In the PURSUIT study, 40 patients who received eptifibatide at the 180/2.0 dosing regimen received a thrombolytic agent, 10 of whom experienced a major bleed.

In another AMI study involving 181 patients, eptifibatide (in regimens up to a bolus of 180 µg/kg followed by a continuous infusion of up to 2.0 µg/kg/min for up to 72 hours) was administered concomitantly with streptokinase (1.5 million units over 60 minutes), another thrombolytic agent. At the highest studied infusion rates (1.3 µg/kg/min and 2.0 µg/kg/min), eptifibatide was associated with an increase in the incidence of bleeding and transfusions compared to the incidence seen when streptokinase was given alone. These limited data on the use of eptifibatide in patients receiving thrombolytic agents do not allow an estimate of the bleeding risk associated with concomitant use of thrombolytics. Systemic thrombolytic therapy should be used with caution in patients who have received eptifibatide.

**Minimization of Vascular and Other Trauma.** Arterial and venous punctures, intramuscular injections, and the use of urinary catheters, nasotracheal intubation, and nasogastric tubes should be minimized. When obtaining intravenous access, non-compressible sites (e.g., subclavian or jugular veins) should be avoided.

**Laboratory Tests.** Before infusion of eptifibatide, the following laboratory tests should be performed to identify pre-existing hemostatic abnormalities: hematocrit or hemoglobin, platelet count, serum creatinine, and PT/aPTT. In patients undergoing PCI, the activated clotting time (ACT) should also be measured.

**Maintaining Target aPTT and ACT.** The aPTT should be maintained between 50 and 70 seconds unless PCI is to be performed. In patients treated with heparin, bleeding can be minimized by close monitoring of the aPTT. Table 7 displays the risk of major bleeding according to the maximum aPTT attained within 72 hours in the PURSUIT study.

**Table 7 Major Bleeding by Maximal aPTT Within 72 Hours in the PURSUIT Study**

	<b>Placebo n(%)</b>	<b>Eptifibatide 180/1.3* n(%)</b>	<b>Eptifibatide 180/2.0 n(%)</b>
Maximum aPTT (seconds)			
<50	44/721 (6.1%)	21/244 (8.6%)	44/743 (5.9%)
50 - 70 (recommended)	92/908 (10.1%)	28/259 (10.8%)	99/883 (11.2%)
>70	281/2786 (10.1%)	99/891 (11.1%)	345/2811 (12.3%)

\* Administered only until the first interim analysis

The ESPRIT study stipulated a target ACT of 200 to 300 seconds during PCI. Patients receiving eptifibatide 180/2.0/180 (mean ACT 284 seconds) experienced an increased incidence of bleeding relative to placebo (mean ACT 276 seconds), primarily at the femoral artery access site. At these lower ACTs, bleeding was less than previously reported with eptifibatide in the PURSUIT and IMPACT II studies.

The aPTT or ACT should be checked prior to arterial sheath removal. The sheath should not be removed unless the aPTT is <45 seconds or the ACT is <150 seconds.

**Thrombocytopenia.** If the patient experiences a confirmed platelet decrease to <100,000/mm<sup>3</sup>, INTEGRILIN and heparin should be discontinued and the condition appropriately monitored and treated.

**Drug Interactions.** Enoxaparin dosed as a 1.0 mg/kg subcutaneous injection q12h for four doses did not alter the pharmacokinetics of eptifibatide or the level of platelet aggregation in healthy adults.

**Geriatric Use.** The PURSUIT and IMPACT II clinical studies enrolled patients up to the age of 94 years (45% were age 65 and over; 12% were age 75 and older). There was no apparent difference in efficacy between older and younger patients treated with eptifibatide. The incidence of bleeding complications was higher in the elderly in both placebo and eptifibatide groups, and the incremental risk of eptifibatide-associated bleeding was greater in the older patients. No dose adjustment was made for elderly patients, but patients over 75 years of age had to weigh at least 50 kg to be enrolled in the PURSUIT study; no such limitation was stipulated in the ESPRIT study (see also ADVERSE REACTIONS).

**Carcinogenesis, Mutagenesis, Impairment of Fertility.** No long-term studies in animals have been performed to evaluate the carcinogenic potential of eptifibatide. Eptifibatide was not genotoxic in the Ames test, the mouse lymphoma cell (L 5178Y, TK+/+) forward mutation test, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Administered by continuous intravenous infusion at total daily doses up to 72 mg/kg/day (about 4 times the recommended maximum daily human dose on a body surface area basis), eptifibatide had no effect on fertility and reproductive performance of male and female rats.

**Pregnancy.** Pregnancy Category B. Teratology studies have been performed by continuous intravenous infusion of eptifibatide in pregnant rats at total daily doses of up to 72 mg/kg/day (about 4 times the recommended maximum daily human dose on a body surface area basis) and in pregnant rabbits at total daily doses of up to 36 mg/kg/day (also about 4 times the recommended maximum daily human dose on a body surface area basis). These studies revealed no evidence of harm to the fetus due to eptifibatide. There are, however, no adequate and well-controlled studies in pregnant women with eptifibatide. Because animal reproduction studies are not always predictive of human response, eptifibatide should be used during pregnancy only if clearly needed.

**Pediatric Use.** Safety and effectiveness of eptifibatide in pediatric patients have not been studied.

**Nursing Mothers.** It is not known whether eptifibatide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when eptifibatide is administered to a nursing mother.

#### **ADVERSE REACTIONS**

A total of 16,782 patients were treated in the Phase III clinical trials (PURSUIT, ESPRIT and IMPACT II). These 16,782 patients had a mean age of 62 years (range 20 to 94 years). Eighty-nine percent of the patients were Caucasian, with the remainder being predominantly Black (5%) and Hispanic (5%). Sixty-eight percent were men. Because of the different regimens used in PURSUIT, IMPACT II and ESPRIT, data from the three studies were not pooled.

**Bleeding.** The incidences of bleeding events and transfusions in the PURSUIT, IMPACT II and ESPRIT studies are shown in Table 8. Bleeding was classified as major or minor by the criteria of the TIMI study group. Major bleeding events consisted of intracranial hemorrhage and other bleeding that led to decreases in hemoglobin greater than 5 g/dL. Minor bleeding events included spontaneous gross hematuria, spontaneous hematemesis, other observed blood loss with a hemoglobin decrease of more than 3 g/dL, and other hemoglobin decreases that were greater than 4 g/dL but less than 5 g/dL. In patients who received transfusions, the corresponding loss in hemoglobin was estimated through an adaptation of the method of Landefeld et al.

**Table 8 Bleeding Events and Transfusions in the PURSUIT, ESPRIT and IMPACT II Studies**

	<b>PURSUIT</b>		
	<b>Placebo n (%)</b>	<b>Eptifibatide 180/1.3* n (%)</b>	<b>Eptifibatide 180/2.0 n (%)</b>
Patients	4696	1472	4679
Major bleeding <sup>a</sup>	425 (9.3%)	152 (10.5%)	498 (10.8%)
Minor bleeding	347 (7.6%)	152 (10.5%)	604 (13.1%)
Requiring Transfusions	490 (10.4%)	188 (12.8%)	601 (12.8%)
	<b>ESPRIT</b>		
	<b>Placebo n (%)</b>	<b>Eptifibatide 180/2.0/180 n (%)</b>	
Patients	1024	1040	
Major bleeding <sup>a</sup>	4 (0.4%)	13 (1.3%)	
Minor bleeding	18 (2.0%)	29 (3.0%)	
Requiring Transfusions	11 (1.1%)	16 (1.5%)	
	<b>IMPACT II</b>		
	<b>Placebo n (%)</b>	<b>Eptifibatide 135/0.5 n (%)</b>	<b>Eptifibatide 135/0.75 n (%)</b>
Patients	1285	1300	1286
Major bleeding <sup>a</sup>	55 (4.5%)	55 (4.4%)	58 (4.7%)
Minor bleeding	115 (9.3%)	146 (11.7%)	177 (14.2%)
Requiring Transfusions	66 (5.1%)	71 (5.5%)	74 (5.8%)

Note: denominator is based on patients for whom data are available

\* Administered only until the first interim analysis

a For major and minor bleeding, patients are counted only once according to the most severe classification.

b Includes transfusions of whole blood, packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets, and autotransfusion during the initial hospitalization.

The majority of major bleeding events in the ESPRIT study occurred at the vascular access site (1 and 8 patients, or 0.1% and 0.8% in the placebo and eptifibatide groups, respectively). Bleeding at "other" locations occurred in 0.2% and 0.4% of patients, respectively. In the PURSUIT study, the greatest increase in major bleeding in eptifibatide-treated patients compared to placebo-treated patients was associated with bleeding at the femoral artery access site (2.8% versus 1.3%). Oropharyngeal (primarily gingival), genito-urinary, gastrointestinal, and retroperitoneal bleeding were also seen more commonly in eptifibatide-treated patients compared to placebo-treated patients. Among patients experiencing a major bleed in the IMPACT II study, an increase in bleeding on eptifibatide versus placebo was observed only for the femoral artery access site (3.2% versus 2.8%).

Table 9 displays the incidence of TIMI major bleeding according to the cardiac procedures carried out in the PURSUIT study. The most common bleeding complications were related to cardiac revascularization (CABG-related or femoral artery access site bleeding). A corresponding table for ESPRIT is not presented as every patient underwent PCI in the ESPRIT study and only 11 patients underwent CABG.

**Table 9 Major Bleeding by Procedures in the PURSUIT Study**

	<b>Placebo n(%)</b>	<b>Eptifibatide 180/1.3* n(%)</b>	<b>Eptifibatide 180/2.0 n(%)</b>
Patients	4577	1451	4604
Overall Incidence of Major Bleeding	425 (9.3%)	152 (10.5%)	498 (10.8%)
Breakdown by Procedure:			
CABG	375 (8.2%)	123 (8.5%)	377 (8.2%)
Angioplasty without CABG	27 (0.6%)	16 (1.1%)	64 (1.4%)
Angiography without Angioplasty or CABG	11 (0.2%)	7 (0.5%)	29 (0.6%)
Medical Therapy Only	12 (0.3%)	6 (0.4%)	28 (0.6%)

Denominators are based on the total number of patients whose TIMI classification was resolved.

\* Administered only until the first interim analysis

In the PURSUIT and ESPRIT studies, the risk of major bleeding with eptifibatide increased as patient weight decreased. This relationship was most apparent for patients weighing less than 70 kg.

Bleeding adverse events resulting in discontinuation of study drug were more frequent among patients receiving eptifibatide than placebo (4.6% versus 0.9% in ESPRIT, 8% versus 1% in PURSUIT; 3.5% versus 1.9% in IMPACT II).

**Intracranial Hemorrhage and Stroke.** Intracranial hemorrhage was rare in the PURSUIT, IMPACT II and ESPRIT clinical studies. In the PURSUIT study, 3 patients in the placebo group, 1 patient in the group treated with eptifibatide 180/1.3 and 5 patients in the group treated with eptifibatide 180/2.0 experienced a hemorrhagic stroke. The overall incidence of stroke was 0.5% in patients receiving eptifibatide 180/1.3, 0.7% in patients receiving eptifibatide 180/2.0, and 0.8% in placebo patients.

In the IMPACT II study, intracranial hemorrhage was experienced by 1 patient treated with eptifibatide 135/0.5, 2 patients treated with eptifibatide 135/0.75 and 2 patients in the placebo group. The overall incidence of stroke was 0.5% in patients receiving 135/0.5 eptifibatide, 0.7% in patients receiving eptifibatide 135/0.75 and 0.7% in the placebo group.

In the ESPRIT study, there were 3 hemorrhagic strokes, 1 in the placebo group and 2 in the eptifibatide group. In addition there was 1 case of cerebral infarction in the eptifibatide group.

**Thrombocytopenia.** In the PURSUIT and IMPACT II studies, the incidence of thrombocytopenia (<100,000/mm<sup>3</sup> or >50% reduction from baseline) and the incidence of platelet transfusions were similar between patients treated with eptifibatide and placebo. In the ESPRIT study, the incidence was 0.6% in the placebo group and 1.2% in the eptifibatide group.

**Allergic Reactions.** In the PURSUIT study, anaphylaxis was reported in 7 patients receiving placebo (0.15%) and 7 patients receiving eptifibatide 180/2.0 (0.16%). In the IMPACT II study, anaphylaxis was reported in 1 patient (0.08%) on placebo and in no patients on eptifibatide. In the PURSUIT study, 2 patients (1 patient (0.04%) receiving eptifibatide and 1 patient (0.08%) receiving placebo) discontinued study drug because of allergic reactions. In the ESPRIT study, there were no cases of anaphylaxis reported. There were 3 patients who suffered an allergic reaction, 1 on placebo and 2 on eptifibatide. In addition, 1 patient in the placebo group was diagnosed with urticaria. The potential for development of antibodies to eptifibatide has been studied in 433 subjects. Eptifibatide was non-antigenic in 412 patients receiving a single administration of eptifibatide (135 µg/kg bolus followed by a continuous infusion of either 0.5 µg/kg/min or 0.75 µg/kg/min), and in 21 subjects to whom eptifibatide (135 µg/kg bolus followed by a continuous infusion of 0.75 µg/kg/min) was administered twice, 28 days apart. In both cases, plasma for antibody detection was collected approximately 30 days after each dose. The development of antibodies to eptifibatide at higher doses has not been evaluated.

**Other Adverse Reactions.** In the PURSUIT and ESPRIT studies, the incidence of serious non-bleeding adverse events was similar in patients receiving placebo or eptifibatide (19% and 19%, respectively in PURSUIT; 6% and 7%, respectively in ESPRIT). In PURSUIT, the only serious non-bleeding adverse event that occurred at a rate of at least 1% and was more common with eptifibatide than placebo (7% versus 6%) was hypotension. Most of the serious non-bleeding events consisted of cardiovascular events typical of an unstable angina population. In the IMPACT II study, serious non-bleeding events that occurred in greater than 1% of patients were uncommon and similar in incidence between placebo- and eptifibatide-treated patients. Discontinuation of study drug due to adverse events other than bleeding was uncommon in the PURSUIT, IMPACT II and ESPRIT studies, with no single event occurring in >0.5% of the study population (except for "other" in the ESPRIT study). In the PURSUIT study, non-bleeding adverse events leading to discontinuation occurred in the eptifibatide and placebo groups in the following body systems with an incidence of >0.1%: cardiovascular system (0.3% and 0.3%), digestive system (0.1% and 0.1%), hemolymphatic system (0.1% and 0.1%), nervous system (0.3% and 0.4%), urogenital system (0.1% and 0.1%), and whole body system (0.2% and 0.2%). In the ESPRIT study, the following non-bleeding adverse events leading to discontinuation occurred in the eptifibatide and placebo groups with an incidence of >0.1%: "other" (1.2% and 1.1%). In the IMPACT II study, non-bleeding adverse events leading to discontinuation occurred in the 135/0.5 eptifibatide and placebo groups in the following body systems with an incidence of >0.1%: whole body (0.3% and 0.1%), cardiovascular system (1.4% and 1.4%), digestive system (0.2% and 0%), hemolymphatic system (0.2% and 0%), nervous system (0.3% and 0.2%), and respiratory system (0.1% and 0.1%).

**Post-Marketing Experience.** The following adverse events have been reported in post-marketing experience, primarily with eptifibatide in combination with heparin and aspirin: cerebral, GI and pulmonary hemorrhage. Fatal bleeding events have been reported. Acute profound thrombocytopenia has been reported.

#### **OVERDOSAGE**

There has been only limited experience with overdosage of eptifibatide. There were 8 patients in the IMPACT II study, 9 patients in the PURSUIT study and no patient in the ESPRIT study who received bolus doses and/or infusion doses more than double those called for in the protocols. None of these patients experienced an intracranial bleed or other major bleeding.

Eptifibatide was not lethal to rats, rabbits, or monkeys when administered by continuous intravenous infusion for 90 minutes at a total dose of 45 mg/kg (about 2 to 5 times the recommended maximum daily human dose on a body surface area basis). Symptoms of acute toxicity were loss of righting reflex, dyspnea, ptosis, and decreased muscle tone in rabbits and petechial hemorrhages in the femoral and abdominal areas of monkeys. From *in vitro* studies, eptifibatide is not extensively bound to plasma proteins and thus may be cleared from plasma by dialysis.

#### **Rx only**

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## L-Arginine After MI Linked to Higher Mortality

The addition of L-arginine to standard post-MI therapy does not decrease vascular stiffness or improve ejection fraction and may be related to increased postinfarction mortality, according to the results of the Vascular Interaction With Age in Myocardial Infarction trial.

Dr. Steven P. Schulman and colleagues randomized 153 patients following a first ST-segment elevation MI to receive L-arginine (with a goal dose of 3 g, three times daily) or placebo. Of the patients, 77 were aged 60 years or older. All the patients were followed up at 1, 3, and 6 months.

The amino acid L-arginine is a substrate for nitric oxide synthase. The results of previous studies suggest that it is associated with a reduction in vascular stiffness.

As such, the investigators' objective was to establish whether the addition of the amino acid to standard treatment in post-MI patients, and especially older patients, would reduce vascular stiffness and improve left ventricular function (JAMA 2006;299:58-64).

In patients aged 60 years and older, ejection fraction and vascular stiffness did not change during the 6 months of follow-up in either group. However, six (9%) patients who had been randomized to L-arginine died, compared with none of those who received placebo. As a result, the data and safety monitoring board closed enrollment, the authors reported.

The participants had normal L-arginine levels at baseline, and Dr. Schulman, an associate professor of medicine and director of the Coronary Care Unit at Johns Hopkins University in Baltimore, and his associates speculated that the L-arginine level could explain the lack of efficacy. "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," the authors wrote, adding that many of the patients were already taking medications such as ACE inhibitors to improve vascular function.

The authors concluded that "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."

—Martha Kerr