# Strong Role Remains for Primary Lytics Early in MI

BY BRUCE JANCIN

Denver Bureau

SNOWMASS, COLO. — The demonstrated superiority of primary percutaneous coronary intervention over fibrinolytics for acute MI in randomized trials has led to a "transfer mania" that is at times counterproductive, Dr. Bernard J. Gersh said at a conference sponsored by the Society for Cardiovascular Angiography and Interventions.

There is solid evidence that the first 2 hours after MI symptom onset represents a golden window of opportunity. Achievement of reperfusion during this window provides far greater myocardial salvage and mortality benefits than at any later time. And the best way to accomplish this in patients who present to community hospitals during this early time period is by urgent administration of intravenous thrombolytic agents, he said.

The delay inherent in transferring such

patients to a facility capable of primary PCI shuts the window of opportunity and moves them into the flatter part of the survival curve. "I find that intellectually indefensible," said Dr. Gersh, professor of medicine at the Mayo Medical School, Rochester, Minn.

He added that it has been known for at least 13 years that thrombolytic therapy is "extraordinarily effective" when given early after symptom onset. The Myocardial Infarction Triage Intervention (MITI) trial showed that 30-day mortality in patients treated within 70 minutes after symptom onset was 1.2%, compared with 8.7% in patients treated later, and that left ventricular infarct size following treatment within 70 minutes of symptom onset was only 4.9%, compared with 11.2% in patients treated later.

More recently, in the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 (ASSENT-3) trial, 25% of aborted MIs as defined by ECG and car-

### Important prescribing and safety considerations

#### Indications for INTEGRILIN Injection:

- For the treatment of patients with acute coronary syndrome (UA/NSTEMI), including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI)
- For the treatment of patients undergoing PCI, including those undergoing intracoronary stenting

#### 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

### Precautions and Warnings:

 In patients undergoing PCI, INTEGRILIN is associated with an increase in major and minor bleeding at the site of arterial sheath placement. Special care should be employed to minimize the risk of bleeding among these patients

- If bleeding cannot be controlled with pressure, infusion of INTEGRILIN and concomitant heparin should be stopped immediately
- Because INTEGRILIN inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis, including thrombolytics, oral anticoagulants, NSAIDs, and dipyridamole
- Use with other GP IIb-IIIa inhibitors should be avoided
- INTEGRILIN is cleared in part by the kidney and its plasma concentrations are doubled in patients with renal disease (creatinine clearance <50 mL/min).</li>
   Therefore, the infusion dose of INTEGRILIN needs to be reduced to 1 mcg/kg/min in these patients.
   INTEGRILIN is contraindicated in patients who are dependent upon renal dialysis (please see dosing guidelines)
- Caution should be exercised when administering INTEGRILIN to patients with a platelet count <100.000/mm<sup>3</sup>
- Bleeding is the most common complication encountered during INTEGRILIN therapy. The majority of excess major bleeding events were localized at the femoral artery access site.
   Oropharyngeal, genitourinary, gastrointestinal, and retroperitoneal bleeding were also seen more commonly with INTEGRILIN compared to placebo

PURSUIT was a multicenter, double-blind, randomized, placebo-controlled study in 10,948 patients presenting with UA or NSTEMI. The primary endpoint was death from any cause or new MI within 30 days of randomization.

ESPRIT was a multicenter, double-blind, randomized, placebo-controlled study that enrolled 2064 patients undergoing elective or urgent PCI with intended intracoronary stent placement. The primary endpoint was the composite of death, MI, urgent target vessel revascularization and "bailout" to open-label INTEGRILIN at 48 hours.

PROTECT TIMI 30 was a randomized trial to evaluate the relative protection against post-PCI microvascular dysfunction and post-PCI ischemia among antiplatelet and antithrombotic agents. Patients were randomized to receive INTEGRILIN plus UFH or enoxaparin or bivalirudin alone. All patients received aspirin plus clopidogrel (300 mg before stenting).

References: 1. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein Ilb/Illa receptor in high-risk coronary angioplasty. N Engl J Med. 1994;330:956–961. 2. Fintel DJ, Ledley GS. Management of patients with non-ST-segment elevation acute coronary syndromes: insights from the PURSUIT trial. Clin Cardiol. 2000;23(suppl V):V-1-V-12. 3. ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet. 2000;356:2037–2044. 4. Horwitz PA, Kimmel SE. Bleeding due to glycoprotein Ilb/Illa receptor inhibition during percutaneous coronary intervention: risk factors and management. Cardiovasc Rev Rep. 2004;25:249–255. 5. The EPILOG Investigators. Platelet glycoprotein Ilb/Illa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med. 1997;336:1689–1696. 6. Data on file, Schering Corporation, 2005.

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PROTECT. PERFUSE. PRESERVE.

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 recommended 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

- IN TEGRILIN® (Eptitionation)
  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 intervience (PCI). In this setting, INTEGRILIN has been shown to decrease the rate of a combined endopinit of death or new invocardial 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 endopinit of death, new myocardial infarction, or need for urgent intervention. In the IMPACT I, PURSUIT and ESPRITI studies of eptitibating, most patients received heparin and aspirin, as described in CLINICAL TRIALS.
  CONTRAINDICATIONS

- CONTRAINDICATIONS

  Treatment with petifibatide 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. 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 Ilb/Illa inhibitor.

  Dependency on renal dialysis.

  Known hypersensitivity to any component of the product.

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- Dependency or neral dialysis.
- Known hypersensitivity to any component of the product.

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	Placebo	Eptifibatide 180/1.3*	Eptifibatide 180/2.0	
	n(%)	n(%)	n(%)	
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%)	

The ESPRIT study stipulated a target ACT of 200 to 300 seconds during PCI. Patients receiving eptifibation 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.

primarily at the femoral artery access site. At these lower ACTs, bleeding was less than previously reported with epitifibatide 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/mm³, 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 epitifibatide 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 epitibatide. The incidence of bleeding complications was higher in the elderly in both placebo and epitificatide groups, and the incremental risk of epitifibatide-associated in the older patients. Or dose adjustment was made for elderly patients, but patients over 75 years of apparent difference in efficacy between older and younger patients treated with epitibatide. The incidence of bleeding was greater in the older patients. No dose adjustment was made for elderly patients, but patients over 75 years of applications 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 epitifibatide. Epitifibatide was not genotoxic in the Armes test, the mouse lymphoma cell (L. 5178/, TK.4/) forward mutation test, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Administered by continuous intravenous infusion of see a sea basis), epitifibatide is administered by continuous intraven

AUVENSE HEACTIONS
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

PURSUIT

	Placedo	180/1.3*	180/2.0	
	n (%)	n (%)	n (%)	
Patients a	4696	1472	4679	
Major bleeding <sup>a</sup>	425 (9.3%)	152 (10.5%)	498 (10.8%)	
Mińor bleeding <sup>a</sup> h	347 (7.6%)	152 (10.5%)	604 (13.1%)	
Requiring Transfusions	490 (10.4%)	188 (12.8%)	601 (12.8%)	
	ESF	PRIT		
	Placebo	Eptifibatide		
		180/2.0/180		
	n (%)	n (%)		
Patients a	1024	1040		
Major bleedinga	4 (0.4%)	13 (1.3%)		
Minor bleeding" h	18 (2.0%)	29 (3.0%)		
Requiring Transfusions	11 (1.1%)	16 (1.5%)		
	IMP	ACT II		
	Placebo	Eptifibatide	Eptifibatide	
		135/0.5	135/0.75	
	n (%)	n (%)	n (%)	
Patients 3	1285	1300	1286	
Major bleedinga	55 (4.5%)	55 (4.4%)	58 (4.7%)	
Minor bleedinga b	115 (9.3%)	146 (11.7%)	177 (14.2%)	
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115 (9.3%) 446 (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

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

Includes transitions of whole blood, packed red blood citsl, 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 0.4% of patients, 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 epitificatioe-treated patients compared to placebo-treated patients was also associated with bleeding at the femoral artery access site (2.8% versus 1.3%). Orophanyngal (primarily ginglava), genito-uniany, gastrointestinal, and retropertonal bleeding were also seen more commonly in epitificatide-treated patients compared to placebo-treated patients. Among patients experiencing a major bleed in the IMPACT II study, an increase in bleeding on epitificatioe versus 2.8%). Table 9 displays the incidence of TIMI major bleeding according to the cardiac procedures carried out in the PURSUIT study. The orons common bleeding complications were related to cardiac revascularization (CABG-related or femoral artery access site bleeding).

Table 9 Major Bleeding by Procedures in the PURSUIT study.

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Table 9 Major Dieeding by Procedures in the Ponson Study							
	Placebo	Eptifibatide 180/1.3*	Eptifibatide 180/2.0				
	n(%)	n(%)	n(%)				
Patients Overall Incidence of Major Bleeding	4577 425 (9.3%)	1451 152 (10.5%)	4604 498 (10.8%)				
Breakdown by Procedure: CABG	375 (8.2%)	123 (8.5%)	377 (8.2%)				
Angioplasty without CABG Angiography without Angioplasty or CABG	27 (0.6%) 11 (0.2%)	16 (1.1%) 7 (0.5%)	64 (1.4%) 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

Denominators are cased on the total number of patients wnose HIMI 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 9.9% in ESPRIT, 8% versus 1% in PURSUIT, 3.5% versus 1.9% in IMPACT II and ESPRIT clinical studies. In the PURSUIT study, 3 patients in the placebo group, 1 patient in the group treated with eptifibatide 18 BNO 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 180/5.7, 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 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 2 patients 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/mm³ or B50% reduction from baseline), and the incidence of platelet transfusions were similar between patients treated with eptifibatide with eptifibatide.

In the ESPHI study, there were 3 reintertratings: trocks, In the placebo group and 2 in the epitihabide group.

Thrombocytopenia. In the PURSUIT and IMPACT II studies, the incidence of thrombocytopenia (<100.000/mm³ or B50% reduction from baseline) and the incidence of platelet transitisons were similar between patients treated with epitihabide and placebo. In the ESPRIT study, the incidence was 0.6% in the placebo group and 1.2% in the epitihabide group.

Allergie Reactions. In the PURSUIT study, anaphylaxis was reported in 7 patients receiving placebo (0.15%) and 7 patients greating placebo (0.15%) and 7 patients seewing epitihabide 180/2.0 (0.15%). In the IMPACT II study, anaphylaxis was reported in 1 patient (0.08%) on placebo and in no patients on epitihabide. In the IMPACT II study, 2 patients (1) applications of anaphylaxis reported in 1 patient (0.08%) receiving placebo) discontinus other study drug because of allergic reactions. In the ESPRITI study, there were no cases of anaphylaxis reported. There were 9 patients were not asset of anaphylaxis reported. There were 9 patients were not asset of anaphylaxis reported. There were 9 patients were not asset of anaphylaxis reported. There were 9 patients were not asset of anaphylaxis reported. There were 9 patients who suffered an allergic reaction, 1 no placebo and 2 on epitihabide in addition, 1 patient in the placebo group was diagnosed with urticaria. The potential for development of antibodies to epitihabide (135 µg/kg bolus followed by a continuous infusion of 0.75 µg/kg/min or 0.75 µg/kg/min), and in 21 subjects to whom epitihabide (135 µg/kg bolus followed by a continuous infusion of 0.75 µg/kg/min or 0.75 µg/kg/min) was administered wice, 28 days apart. In both cases, plasma for antibody detection was collected approximately 30 days after each dose. The development of antibodies to epitihabide (135 µg/kg bolus followed by a continuous infusion of 0.75 µg/kg/min or 0.75 µg/kg/min) was administered wice, 28 days apart. In both cases, plasma for antibo

OVEROÖSAGE

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 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 loxicity were loss of righting reflex, dyspnea, ptosis, and decreased muscle tone in rabbits and petechal 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.

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Issued June 2005 Rev 11

## 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;259:58-64).

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.'