(eptifibatide) Injection

INTEGRILIN®

PROTECT. PERFUSE. PRESERVE.

## Did You Know?

- List the 2 indications for INTEGRILIN® (eptifibatide).
- In the clinical trials that showed INTEGRILIN to be effective, all patients received concomitant therapy with 2 other agents. What were they?

Answer 1

1. For the treatment of patients with acute coronary syndrome (ACS) (unstable angina/non–ST-segment elevation myocardial infarction), including patients who are to be managed medically, and those undergoing percutaneous coronary intervention (PCI).
2. For the treatment of patients undergoing PCI, including patients undergoing intracoronary stenting.

Answer 2

Aspirin and heparin.

## Did You Know?

- The CLEAR PLATELETS trial showed that INTEGRILIN® (eptifibatide) increased platelet aggregation inhibition when added to what other agent?

- In patients with impaired renal function (CrCl <50 mL/min), the infusion part of the INTEGRILIN dose should be reduced to _____.

Answer 3

Plavix® (clopidogrel).

Answer 4

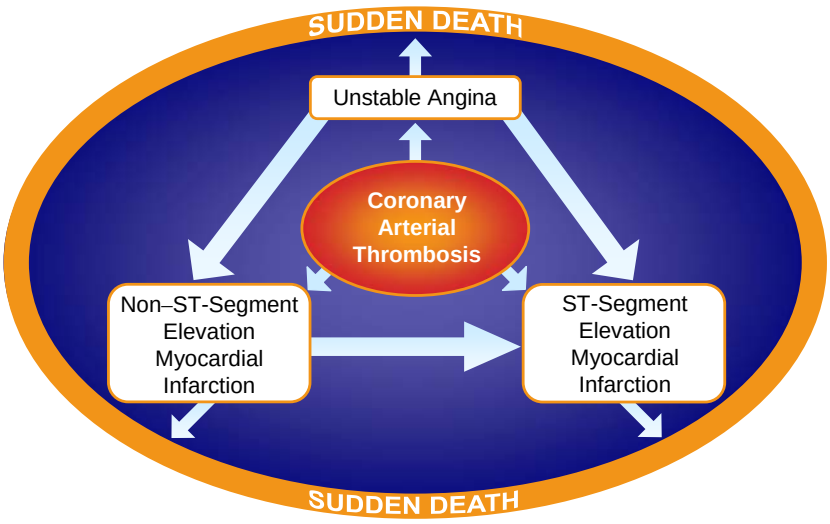
1.0 mcg/kg/min (by half).

## Learning Objectives

- Define ACS (UA/NSTEMI) and review pharmacologic options
- Understand the recommendations of the ACC/AHA Practice Guidelines for the management of ACS (UA/NSTEMI)
- Review clinical benefits of GP IIb-IIIa inhibitors and INTEGRILIN® (eptifibatide) in ACS (UA/NSTEMI) and PCI
- Review dosing and administration of INTEGRILIN

- This slide presentation begins with a definition of the pathophysiology of acute coronary syndrome (ACS), including a brief overview of pharmacologic options for managing ACS (UA/NSTEMI)
- The next section reviews the clinical benefits of the class of agents known as glycoprotein (GP) IIb-IIIa inhibitors, with a focus on clinical trial data for INTEGRILIN, a potent GP IIb-IIIa inhibitor indicated for the treatment of patients being medically managed for ACS (UA/NSTEMI) and patients undergoing percutaneous coronary intervention (PCI)
- The last section presents information on the dosing and administration of INTEGRILIN

## Acute Coronary Syndrome (ACS)




Van de Werf F. *Thromb Haemost.* 1997;78:210–213.

Acute coronary syndromes share one common pathophysiologic mechanism:

Plaque rupture, which leads to platelet activation, which leads to thrombus formation.

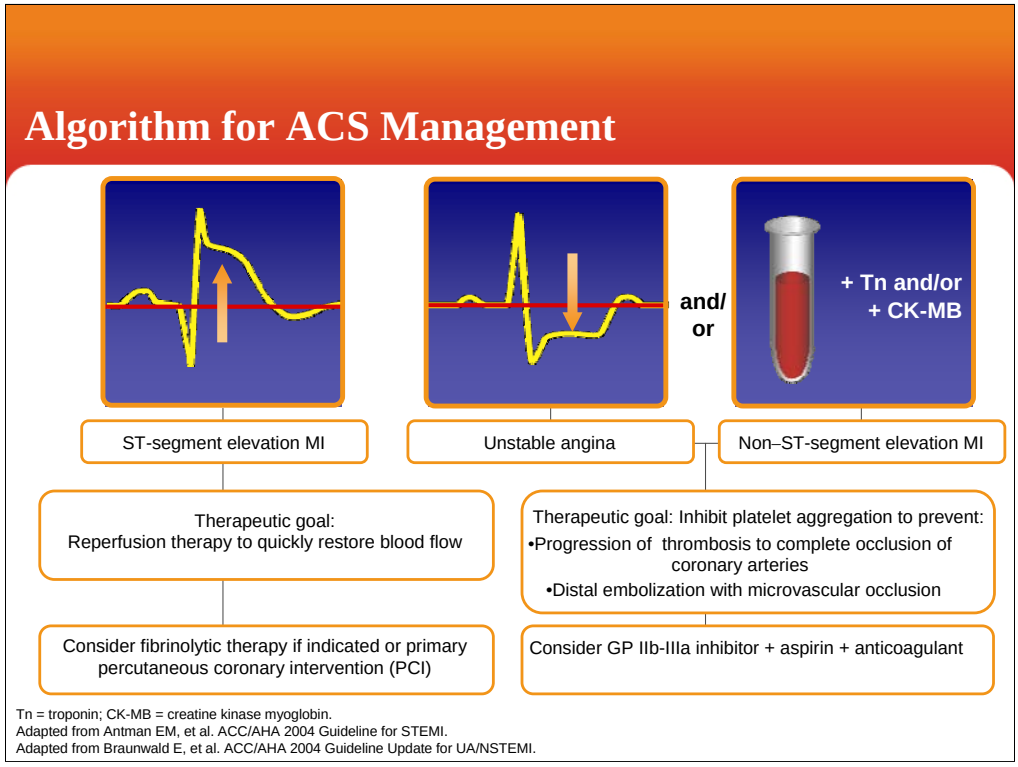
Disruption of plaque can result in a number of clinical syndromes[1]:

- Unstable angina (UA)
- Non–ST-segment elevation myocardial infarction (NSTEMI)
- ST-segment elevation myocardial infarction (STEMI)

In ACS, platelet aggregation leads to the formation of nonocclusive coronary thrombi, which clinically manifest as unstable angina—or, if prolonged with occlusion, results in myocardial damage as NSTEMI. NSTEMI may be caused by dislodgement and embolization of platelet-rich microthrombi into the coronary microvasculature, blocking blood flow and causing heart muscle death. Complete occlusion of the arteries manifests clinically as STEMI.[2]

---

1. Van de Werf F. Clinical trials with glycoprotein IIb/IIIa receptor antagonists in acute coronary syndromes. *Thromb Haemost*. 1997;78:210–213.
2. White HD. Unmet therapeutic needs in the management of acute ischemia. *Am J Cardiol.* 1997;80:2B–10B.




This algorithm for the management of acute coronary syndrome (ACS) is based on the recommendations of practice guidelines issued jointly by the American College of Cardiology (ACC) and the American Heart Association (AHA).

ST-segment elevation myocardial infarction (STEMI) is diagnosed by ECG changes consistent with ST-segment elevation and by the presence of serum biomarkers of cardiac damage, especially troponin (Tn).[1]

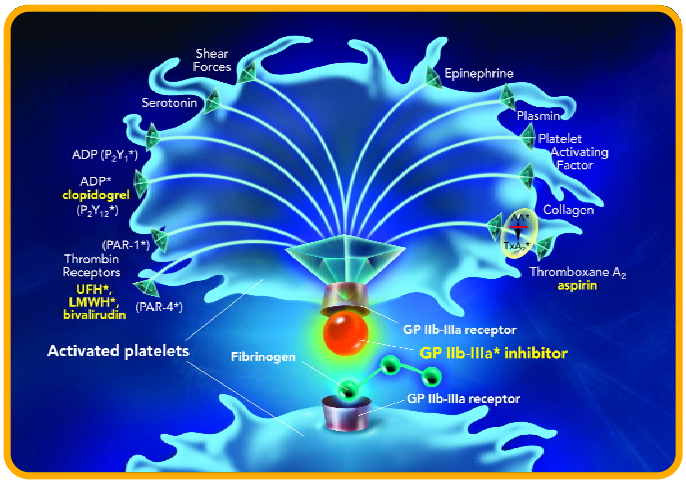
Non–ST-segment elevation myocardial infarction (NSTEMI) is diagnosed by ECG changes consistent with the absence of ST-segment elevation. Initially, a patient whose ECG shows ST-segment depression is considered to have either unstable angina (UA) or NSTEMI; ultimately, the difference between these 2 diagnoses is based on blood tests detecting certain markers of myocardial necrosis, including Tn and creatine kinase myoglobin (CK-MB).[2]

The ACC/AHA Guidelines for the management of patients with UA/NSTEMI recommend administering a GP IIb-IIIa inhibitor plus aspirin to inhibit platelet aggregration, as well as an anticoagulant in patients undergoing catheterization and percutaneous coronary intervention (PCI).[2]

---

1. Adapted from Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction. Available at: http://www.acc.org/clinical/guidelines/stemi/index.pdf. Accessed February 21, 2006.
2. Adapted from Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). Available at: http://www.acc.org/clinical/guidelines/unstable/unstable.pdf. Accessed February 21, 2006.

## GP IIb-IIIa Receptor: The Final Common Pathway to Platelet Aggregation




*ADP=Adenosine diphosphate; GP IIb-IIIa=Glycoprotein IIb-IIIa; LMWH=Low-molecular-weight heparin; $P_2Y_1$ and $P_2Y_{12}$=Purinoreceptors for ADP; PAR-1=Protease-activated receptor-1; PAR-4=Protease-activated receptor-4; $TxA_2$=Thromboxane $A_2$; UFH=Unfractionated heparin.

White HD. *Am J Cardiol.* 1997;80:2B–10B; Schafer A, et al. *J Clin Invest*. 1986;78:73–79; De Jong MJ, et al. *Crit Care Nurs Clin North Am.* 1999;11:355–371. Lefkovits J, Topol EJ. *Eur Heart J*. 1996;17:9–18. Wagner CL, et al. *Blood.* 1996;88:907–914.

There are more than 90 known platelet agonists; among them are thrombin, adenosine diphosphate (ADP), collagen, serotonin, and epinephrine. Each of these agonists activates a separate signal transduction pathway within platelets. All of these pathways ultimately converge on the platelet receptor glycoprotein (GP) IIb-IIIa, converting it from an inactive into an active form.[1,2]

Antithrombin agents—such as direct thrombin inhibitors (eg, bivalirudin) and agents that act via antithrombin III (eg, unfractionated heparin [UFH] and low-molecular-weight heparin [LMWH])—reduce the formation of fibrin-rich mesh necessary for the generation of completely occlusive thrombi.[1,3] Clopidogrel, a thienopyridine, inhibits ADP.[4] Aspirin inhibits cyclooxygenase-1 within platelets and prevents the formation of thromboxane $A_2$ ($TxA_2$). However, these agents may not optimally inhibit platelet aggregation, because there are many platelet agonists.[1]

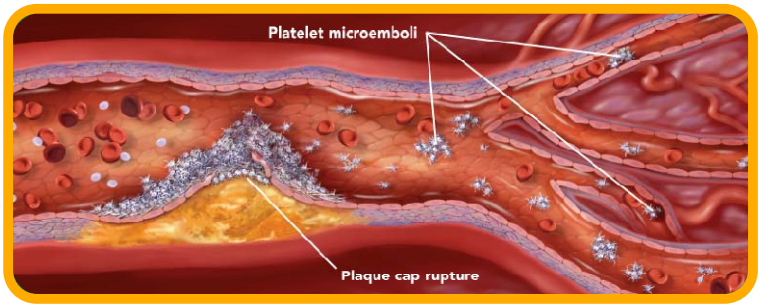
The platelet receptor GP IIb-IIIa is the final common pathway to platelet aggregation, which involves binding of a single molecule of fibrinogen to two GP IIb-IIIa molecules on the surface of adjacent platelets.[1]

Only GP IIb-IIIa inhibitors block this receptor directly, preventing platelet aggregation, regardless of the agonist.[1]

---


1. White HD. Unmet therapeutic needs in the management of acute ischemia. *Am J Cardiol.* 1997;80:2B–10B.
2. De Jong MJ, Wright SL. New adjunctive therapy for ischemic syndrome. *Crit Care Nurs Clin North Am*. 1999;11:355–371.
3. Angiomax® (bivalirudin) Prescribing Information.
4. Plavix® (clopidogrel) Prescribing Information.

# The Use of Antiplatelet and Anticoagulant Agents in the Setting of NSTE ACS




**GP IIb-IIIa inhibitors** prevent platelet aggregation and improve perfusion to the microvasculature.

**Aspirin, thienopyridines, and anticoagulants** each block a single pathway (thromboxane $A_2$, ADP, and thrombin, respectively) to inhibit platelet activation.

**Aspirin** blocks inflammatory activities that could further destabilize plaque.

Collet JP, et al. Structural and dynamic investigation of the facilitating effect of glycoprotein IIb/IIIa inhibitors in dissolving platelet-rich clots. *Circ Res*. 2002;90:428-434; Moser M, et al. *J Cardiovasc Pharmacol*. 2003;41(4):586-592; White HD. *Am J Cardiol*. 1997;80(4A):2B-10B; DeJong MJ, et al. *Crit Care Nurs Clin North Am*. 1999;11(3):355-371.

Antithrombotic therapies include aspirin; thienopyridines (clopidogrel and ticlopidine); anticoagulants (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], and bivalirudin; and glycoprotein (GP) IIb-IIIa inhibitors (eptifibatide, abciximab, and tirofiban).[1]

Anticoagulants target thrombin; they partially prevent platelet activation, aggregation, and thrombus progression.[1]

Subacute platelet activation inhibitors block one agonist of platelet activation; for example:

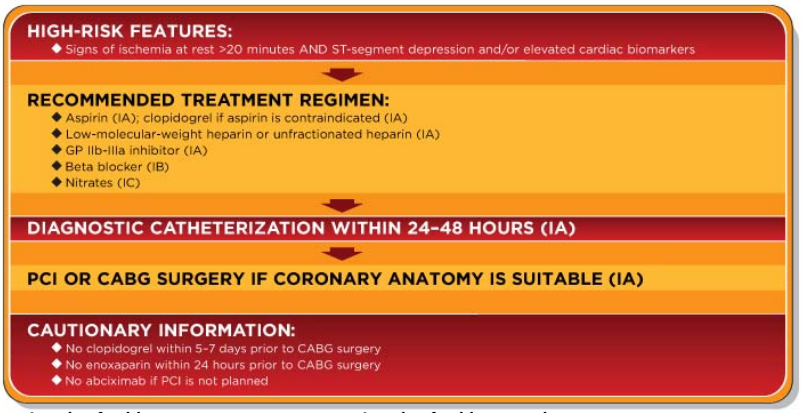
- Clopidogrel (a thienopyridine) inhibits adenosine diphosphate (ADP)[2]
- Aspirin inhibits cyclooxygenase-1 within platelets and prevents the formation of thromboxane $A_2$ ($TxA_2$)[3]
- Aspirin blocks inflammatory activities that could further destabilize plaque

The antithrombotic activity provided by the GP IIb-IIIa inhibitors goes beyond that provided by anticoagulants and oral antiplatelet agents. GP IIb-IIIa inhibitors prevent platelet aggregation, regardless of the agonist, and improve perfusion to the microvasculature.[1]

---

1. White HD. Unmet therapeutic needs in the management of acute ischemia. *Am J Cardiol.* 1997;80(4A):2B–10B.
2. Plavix® (clopidogrel) Prescribing Information.
3. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). Available at: http://www.acc.org/clinical/guidelines/unstable/unstable.pdf. Accessed February 21, 2006.

# GP IIb-IIIa Inhibitors Are an ACC/AHA Guidelines IA Recommendation




**Levels of evidence:**

I. Evidence and/or agreement that treatment is effective
IIa. Weight of evidence favors use
IIb. Usefulness less well established
III. Evidence and/or agreement that treatment is not effective

**Levels of evidence ranks:**

A. Based on large, randomized trials
B. Based on smaller trials or careful analyses
C. Based on expert consensus

Adapted from Braunwald E, et al. ACC/AHA 2002 Guideline Update for UA/NSTEMI.
Smith SC Jr, et al. ACC/AHA/SCAI 2005 Guideline Update for PCI.

The ACC/AHA Guidelines provide a strong, evidence-based IA recommendation for the use of GP IIb-IIIa inhibitors as part of an overall antiplatelet/antithrombotic treatment strategy in patients with UA/NSTEMI. The Guidelines recommend early, aggressive treatment of UA/NSTEMI.[1]

- Antiplatelet therapy should be initiated promptly (Level IA)
- A GP IIb-IIIa inhibitor plus and anticoagulant (UFH, LMWH) should be administered to patients undergoing PCI (Level IA)
- A GP IIb-IIIa inhibitor plus and anticoagulant should be administered to patients with continuing ischemia, elevated troponin, or other high-risk features who will not undergo invasive management strategies (Level IIa)

Note that the administration of clopidogrel is not recommended 5 to 7 days prior to CABG.[2]

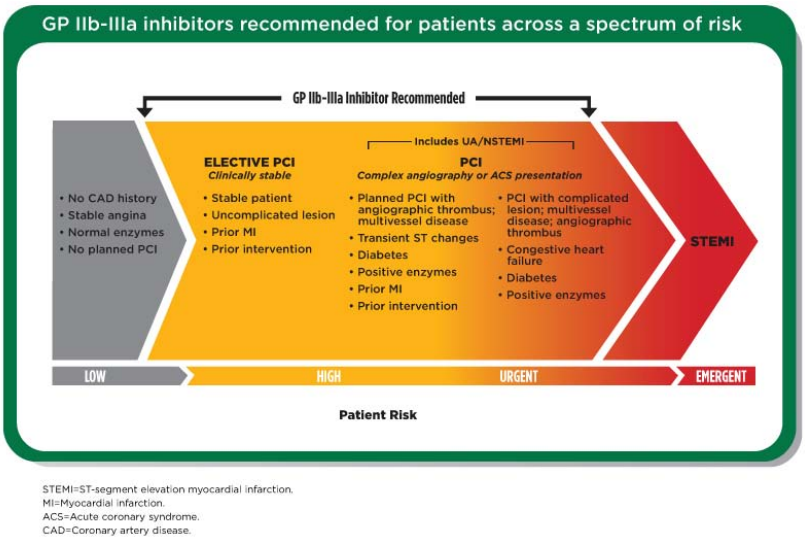
IA = I. Evidence and/or agreement that treatment is effective; A. Based on large, randomized trials.

IIa = Weight of evidence favors use.

---


1. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). Available at: http://www.acc.org/clinical/guidelines/unstable/unstable.pdf. Accessed February 21, 2006.
2. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Available at: http://www.acc.org/clinical/guidelines/percutaneous/update/index_rev.pdf. Accessed February 21, 2006.

# GP IIb-IIIa Inhibitors Recommended for Patients Across a Spectrum of Risk




Smith SC, et al. ACC/AHA/SCAI 2005 Guideline Update for PCI.

The ACC/AHA/SCAI Guidelines for percutaneous coronary intervention recommend the use of GP IIb-IIIa inhibitors in patients undergoing PCI—ranging from patients who are clinically stable to those who have complex angiography or ACS presentation.

_____

Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Available at: http://www.acc.org/clinical/guidelines/percutaneous/update/index_rev.pdf. Accessed February 21, 2006.

# Complex Anatomies Put PCI Patients at Risk for Major Complications

Complicated lesions

Angulated segment

Excessive tortuosity

Multivessel disease

Inability to protect major sidebranches

Angiographic thrombus

Smith SC, et al. ACC/AHA/SCAI 2005 Guideline Update for PCI.

Click on each road sign to view an illustration of the complex anatomies that can put PCI patients at risk for major complications.

Patients undergoing elective percutaneous coronary intervention (PCI) are at risk for MI and other major complications if they have certain complex anatomical features. The physician should be prepared for any of the following signs of high risk: complicated lesions, angulated segment, excessive tortuosity, multivessel disease, inability to protect major sidebranches, and angiographic thrombus.

---

Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Available at: http://www.acc.org/clinical/guidelines/percutaneous/update/index_rev.pdf. Accessed February 21, 2006.

# INTEGRILIN® (eptifibatide): Indications and Usage

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

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

INTEGRILIN is indicated:

- For the treatment of patients with acute coronary syndrome (unstable angina/non–ST-segment elevation myocardial infarction [UA/NSTEMI]), 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 (MI), or need for urgent intervention

Most patients received heparin and aspirin in the pivotal clinical trials of INTEGRILIN (PURSUIT, ESPRIT, and IMPACT II).

---

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

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.

# INTEGRILIN® (eptifibatide): PK and PD Properties

- Specific for platelet receptor GP IIb-IIIa
- Potent inhibitor of platelet aggregation
- Onset of platelet aggregation inhibition within 15 minutes
- Reversible — restoration of platelet function toward baseline (<50% inhibition) within 4 hours of discontinuation of infusion
- Eptifibatide and its metabolites primarily renally excreted
- Plasma elimination half-life of approximately 2.5 hours

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

Human pharmacodynamic data for INTEGRILIN were obtained in healthy subjects and in patients presenting with UA/NSTEMI and/or undergoing PCI. In 2 pivotal studies, IMPACT II* and PURSUIT,† INTEGRILIN exhibited the following pharmacodynamic and pharmacokinetic properties[1]**:**

- The effect of INTEGRILIN was observed after administration of a 180-mcg/kg IV bolus
- The initial onset of inhibition of platelet aggregation was observed within 15 minutes after an IV bolus*†
- The action of INTEGRILIN is reversible: platelet function was restored toward baseline (<50% inhibition) within 4 hours of discontinuation of infusion
- In contrast, Plavix® (clopidogrel) acts by irreversibly modifying the platelet adenosine diphosphate (ADP) receptor. In cases that require quick reversal of the pharmacological effects of clopidogrel, platelet transfusion is recommended if it is biologically plausible[2]
- Eptifibatide and its metabolites are primarily renally excreted[1]
- The plasma elimination half-life of INTEGRILIN is approximately 2.5 hours[1]

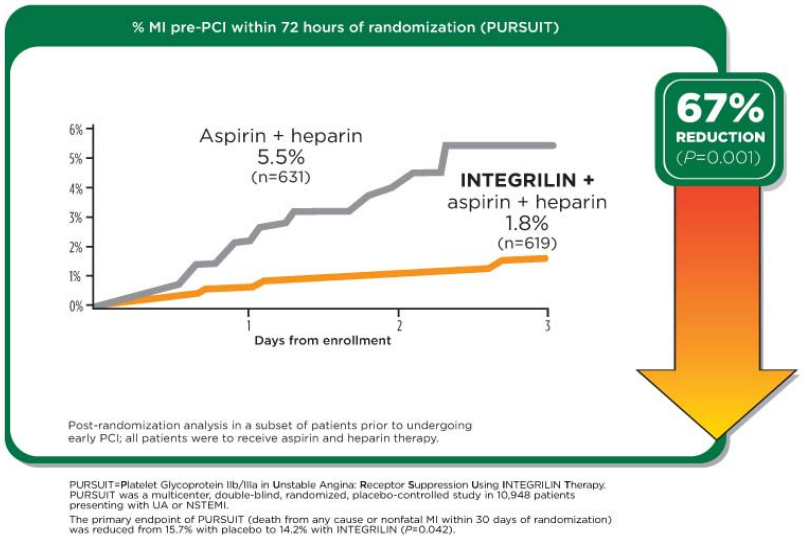
*IMPACT II = **I**NTEGRILIN to **Mi**nimize **P**latelet **A**ggregation and Prevent **C**oronary **T**hrombosis II.
In IMPACT II, INTEGRILIN was administered as a 135-mcg/kg bolus followed by a continuous infusion of 0.5 mcg/kg/min.

†PURSUIT = **P**latelet Glycoprotein IIb/IIIa in **U**nstable Angina: **R**eceptor **S**uppression **U**sing **I**NTEGRILIN **T**herapy.
In PURSUIT, INTEGRILIN was administered as a 180-mcg/kg bolus followed by a continuous infusion of 2.0 mcg/kg/min.

1. INTEGRILIN® (eptifibatide) Injection Prescribing Information.
2. Plavix® (clopidogrel) Prescribing Information.

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.

# INTEGRILIN® (eptifibatide) Achieved Significant Risk Reduction Before Starting PCI




PURSUIT=Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using INTEGRILIN Therapy. PURSUIT was a multicenter, double-blind, randomized, placebo-controlled study in 10,948 patients presenting with UA or NSTEMI.
The primary endpoint of PURSUIT (death from any cause or nonfatal MI within 30 days of randomization) was reduced from 15.7% with placebo to 14.2% with INTEGRILIN (*P*=0.042).

Fintel DJ, et al. *Clin Cardiol*. 2000;23:V-1–V-12.

In the PURSUIT (**P**latelet Glycoprotein IIb/IIIa in **U**nstable Angina: **R**eceptor **S**uppression **U**sing **I**NTEGRILIN **T**herapy) study, MI occurred within 72 hours of randomization in 5.5% of patients receiving only aspirin plus heparin (n=631) and in only 1.8% of patients receiving aspirin plus heparin plus INTEGRILIN (n=619).

This 67% reduction (*P*=0.001) was evident even before patients underwent PCI.

**Study Design**

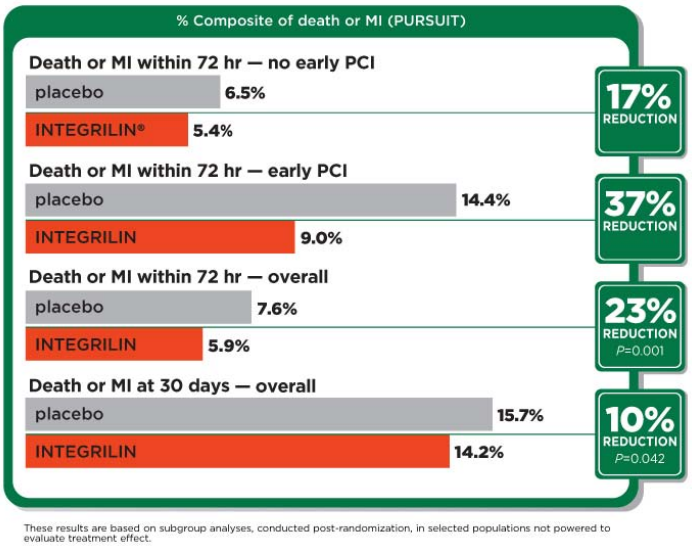
- PURSUIT was a double-blind, randomized, placebo-controlled study of 10,948 patients with UA or NSTEMI at 726 hospitals in the United States, Canada, and 25 countries throughout Europe and Latin America
- PURSUIT was undertaken to evaluate the safety and efficacy of INTEGRILIN in combination with standard antithrombotic therapy (aspirin and UFH) in the context of “real-world” management of patients with NSTEMI
- The primary endpoint of PURSUIT was death from any cause or nonfatal MI within 30 days of randomization
- Patients were randomized in a double-blind fashion to receive 1 of 3 regimens:
  - Placebo (bolus + infusion)
  - INTEGRILIN 180-mcg/kg bolus plus INTEGRILIN 1.3-mcg/kg/min infusion
  - INTEGRILIN 180-mcg/kg bolus plus INTEGRILIN 2.0-mcg/kg/min infusion
- Duration of study drug varied; the INTEGRILIN infusion was to be administered until either discharge from the hospital or initiation of CABG surgery, up to a maximum of 72 hours
- All patients received therapy with aspirin, heparin, or both

---

Fintel DJ, Ledley GS, eds. Management of patients with non–ST-segment elevation acute coronary syndromes: insights from the PURSUIT Trial. *Clin Cardiol.* 2000;23:V-1–V-12.

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.

## Ischemic Reduction Regardless of Management Strategy




Fintel DJ, et al. *Clin Cardiol*. 2000;23:V-1–V-12.

The primary endpoint of PURSUIT (death from any cause or nonfatal MI within 30 days of randomization) was reduced from 15.7% with placebo to 14.2% with INTEGRILIN (*P*=0.042).

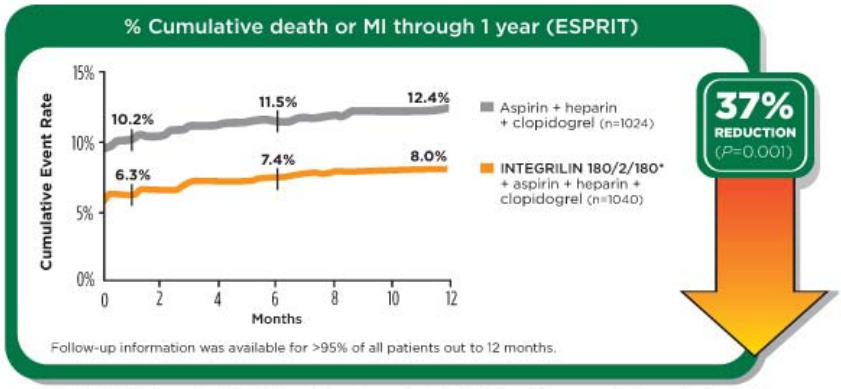
In a subanalysis of the PURSUIT trial, early use of INTEGRILIN reduced the risk of death or MI vs aspirin and heparin alone, regardless of management strategy. This included patients who received diagnostic catheterization, revascularization (PCI or CABG surgery), or continued to receive medical management alone.

---

Fintel DJ, Ledley GS. Management of patients with non–ST-segment elevation acute coronary syndromes: insights from the PURSUIT trial. *Clin Cardiol*. 2000;23:V-1–V-12.

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.

# INTEGRILIN® (eptifibatide): Significant Event Reductions Maintained Long After PCI




*180/2/180=180-mcg/kg bolus followed by a 2-mcg/kg/min infusion, with a second 180-mcg/kg bolus 10 minutes after the first bolus.
ESPRIT=**E**nhanced **S**uppression of the **P**latelet IIb/IIIa **R**eceptor with **I**NTEGRILIN **T**herapy.
ESPRIT was a randomized, double-blind, placebo-controlled, parallel-group study in 2064 patients scheduled to undergo PCI.

O'Shea JC, et al. *JAMA*. 2002;287(5):618–621.

The primary composite endpoint of the ESPRIT (**E**nhanced **S**uppression of the **P**latelet IIb/IIIa **R**eceptor with **I**NTEGRILIN **T**herapy) study (death, MI, urgent target vessel revascularization [UTVR], or thrombotic bailout within 48 hours) was reduced from 10.5% with placebo to 6.6% (37% reduction) with INTEGRILIN (*P*=0.0015).

Twelve-month follow-up data (available for more than 95% of all patients) showed that the reduction in ischemic complications of PCI with stent implantation was sustained through 1 year.

**Study Design**

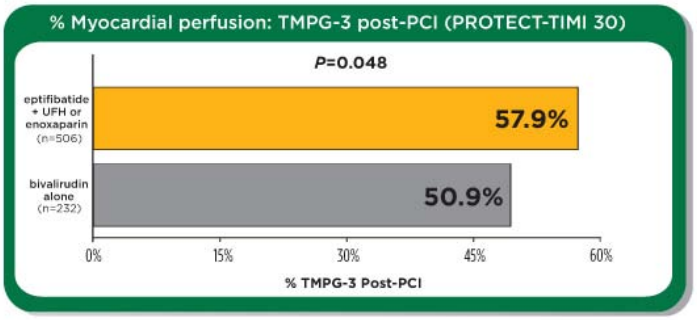
- ESPRIT was a multicenter, double-blind, randomized, placebo-controlled parallel-group, crossover-permitted study that enrolled 2064 patients in the United States and Canada who were undergoing PCI with intended intracoronary stent implantation
- The primary endpoint of ESPRIT was the composite of death, MI, UTVR, and bailout to open-label INTEGRILIN due to a thrombotic complication of PCI at 48 hours
- Patients received a wide variety of stents; drug treatment began immediately prior to PCI. Patients were randomized to either placebo or INTEGRILIN (given as two 180-mcg/kg boluses 10 minutes apart, and as a continuous infusion of 2.0 mcg/kg/min). The INTEGRILIN infusion was continued for 18 to 24 hours after PCI or until hospital discharge, whichever came first
- All patients also received concomitant aspirin and a weight-adjusted heparin regimen. Patients were also allowed to receive treatment with a thienopyridine (either clopidogrel or ticlopidine) on the day of stent implantation, but not before

---

O'Shea JC, Buller CE, Cantor WJ, et al. Long-term efficacy of platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention. *JAMA*. 2002;287(5):618–621.

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.

## Myocardial Perfusion: INTEGRILIN® (eptifibatide) + UFH/enoxaparin vs Bivalirudin Alone




TMPG=TIMI myocardial perfusion grade.

PROTECT-TIMI 30=**PROTECT**ion Against Post-PCI Microvascular Dysfunction, Ischemia and Inflammation among Anti-Platelet and Anti-Thrombotic Agents.
PROTECT-TIMI 30 was a randomized trial to evaluate the relative protection against post-PCI microvascular dysfunction and post-PCI ischemia with INTEGRILIN + UFH/enoxaparin or with bivalirudin alone. All patients received aspirin plus clopidogrel (300 mg before stenting).

Gibson CM, et al. In press.

In angiographically evaluable patients, the primary endpoint of post-PCI coronary flow reserve (CFR) was higher in the bivalirudin arm (1.43 vs 1.33; *P*=0.036). However, when all patients were evaluated (including those with abrupt closure, occluded artery, or thrombotic bailout), CFR was not significantly different between treatment arms (*P*=0.13).

In the PROTECT study, INTEGRILIN + UFH/enoxaparin significantly improved myocardial perfusion vs bivalirudin alone, as measured by TIMI Myocardial Perfusion Grade (TMPG).

**Study Design**

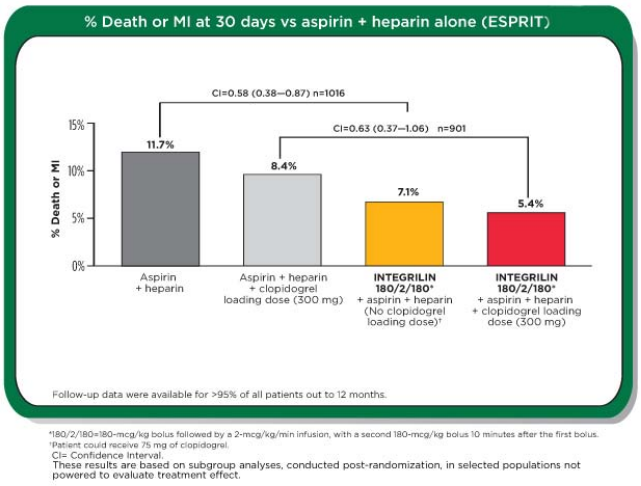
- PROTECT-TIMI 30 was a randomized open-label, parallel-group, multcenter, international study to evaluate the relative protection against post-PCI microvascular dysfunction and post-PCI ischemia among antiplatelet and antithrombotic agents
- The primary endpoint, CFR, is a measure of the capacity of blood flow to be augmented in response to intracoronary adenosine (hyperemic flow). CFR was assessed using the Corrected TIMI Frame Count (CTFC)
- Patients were randomized to receive INTEGRILIN + UFH or enoxaparin or bivalirduin alone. Patients taking UFH received 50-U/kg bolus with a target ACT of 200 to 250 seconds. All patients received aspirin plus clopidogrel (300 mg) before stenting

---

Gibson CM, Morrow DA, Murphy SA, et al, for the TIMI Study Group. A randomized trial to evaluate the Relative PROTECTion Against Post-PCI Microvascular Dysfunction, Ischemia and Inflammation Among Anti-Platelet and Anti-Thrombotic Agents: The PROTECT-TIMI Trial. In press.

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.

# INTEGRILIN® (eptifibatide) Ischemic Events Alone or in Combination




The primary composite endpoint of the ESPRIT study (death, MI, urgent target vessel revascularization [UTVR], or thrombotic bailout within 48 hours) was reduced from 10.5% with placebo to 6.6% (37% reduction) with INTEGRILIN (*P*=0.0015).
The key secondary endpoint for ESPRIT was the composite of death,
MI, and UTVR at 30 days; placebo 10.% vs eptifibatide 6.8% (P=0.003).
ESPRIT = **E**nhanced **S**uppression of the **P**latelet IIb/IIIa **R**eceptor with **I**NTEGRILIN **T**herapy.
Data on file, Schering-Plough.

This data from ESPRIT (**E**nhanced **S**uppression of the **P**latelet IIb/IIIa **R**eceptor with **I**NTEGRILIN **T**herapy) shows the rate of ischemic events when INTEGRILIN was added to aspirin/heparin, with or without a clopidogrel loading dose.

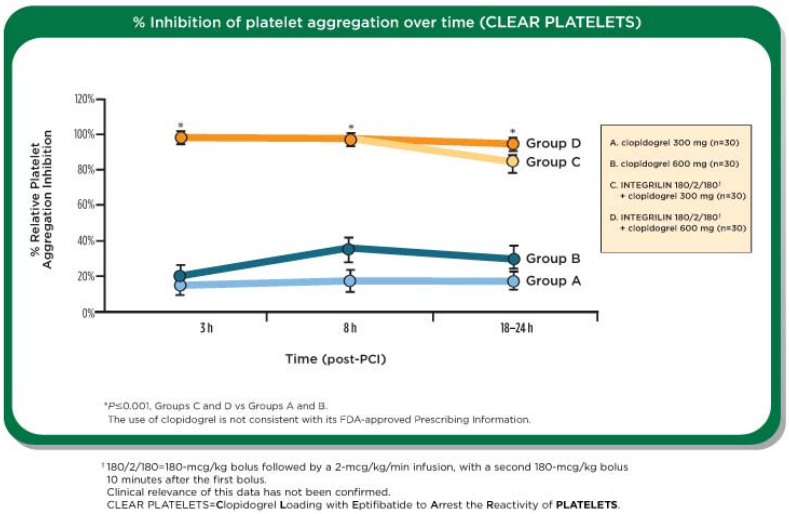
**Study Design**

- ESPRIT enrolled 2064 patients who were undergoing stent implantation
- Patients were randomized to receive either INTEGRILIN or placebo. Each patient also received at least 1 dose of aspirin (162–325 mg) and a weight-adjusted heparin regimen. Patients were also allowed to receive clopidogrel or ticlopidine (60 U/kg) on the day of stent implantation
- Follow-up data for ESPRIT were obtained by clinic visit or telephone contact out to 12 months after randomization
- These results are based on subgroup analyses, conducted post-randomization, in selected populations not powered to evaluate treatment effect
- In this post-randomization subanalysis of ESPRIT, the endpoints of death/MI were compared for aspirin + heparin vs INTEGRILIN + aspirin + heparin and aspirin + heparin + clopidogrel loading dose vs INTEGRILIN + aspirin + heparin + clopidogrel loading dose. The rates of death/MI were 11.7% vs 7.1% (OR, 0.58 [95% CI, 0.38–0.87]) and 8.4% vs 5.4% (OR, 0.63 [95% CI, 0.37–1.06), respectively

Data on file, Schering-Plough.

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.

# INTEGRILIN® (eptifibatide) Greater Inhibition of Platelet Aggregation vs Clopidogrel Alone




†180/2/180=180-mcg/kg bolus followed by a 2-mcg/kg/min infusion, with a second 180-mcg/kg bolus 10 minutes after the first bolus.
Clinical relevance of this data has not been confirmed.
CLEAR PLATELETS=**C**lopidogrel **L**oading with **E**ptifibatide to **A**rrest the **R**eactivity of **PLATELETS**.

Gurbel PA, et al. *Circulation*. 2005; 111:1153–1159.

In CLEAR PLATELETS (**C**lopidogrel **L**oading with **E**ptifibatide to **A**rrest the **R**eactivity of **PLATELETS**), the addition of INTEGRILIN significantly increased the level of platelet aggregation inhibition of clopidogrel 300 and 600 mg at 3, 8, and 18 to 24 hours after stenting (*P*<0.001).

**Study Design**

- CLEAR PLATELETS was a prospective, randomized, pharmacodynamic investigation to compare the antiplatelet effects of standard-dose and high-dose clopidogrel, with and without INTEGRILIN. The study involved 120 patients undergoing elective coronary artery stenting
- Patients were randomly assigned to 1 of 4 treatment regimens after stent implantation:
  - Clopidogrel 300 mg
  - Clopidogrel 600 mg
  - INTEGRILIN plus clopidogrel 300 mg
  - INTEGRILIN plus clopidogrel 600 mg
- Platelet reactivity was assessed by aggregometry and flow cytometry

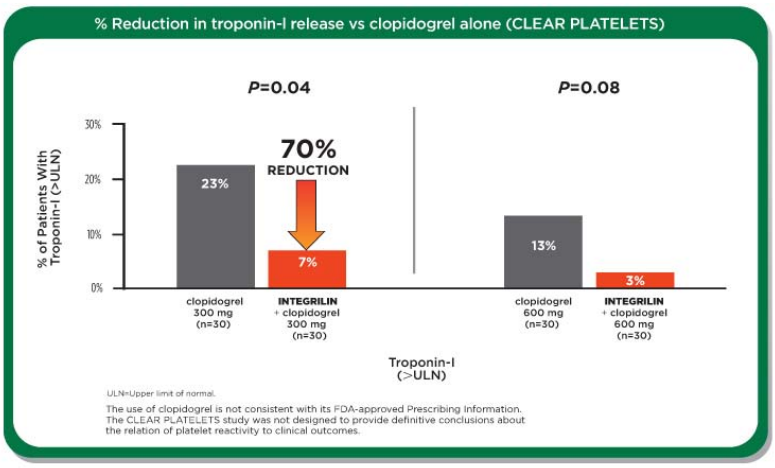
**Note*:*** Clinical relevance of this data has not been confirmed.

---

Gurbel PA, Bliden KP, Zaman KA, Yoho JA, Hayes KM, Tantry US. Clopidogrel loading with eptifibatide to arrest the reactivity of platelets. Results of the Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study. *Circulation.* 2005;111:1153–1159.

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.

# INTEGRILIN® (eptifibatide) Significantly Reduced Troponin-I Release When Added to Clopidogrel 300 mg




Gurbel PA, et al. *Circulation*. 2005;111:1153–1159.

CLEAR PLATELETS also showed that INTEGRILIN significantly reduced the release of troponin-I (a marker for myocardial necrosis) when added to clopidogrel 300 mg (the standard loading dose).

Troponin-I release for patients receiving clopidogrel 300 mg was 23% for clopidogrel alone vs 7% when INTEGRILIN was added. For patients receiving clopidogrel 600 mg, troponin-I release was 13% for clopidogrel alone vs 3% when INTEGRILIN was added (*P*=0.08).

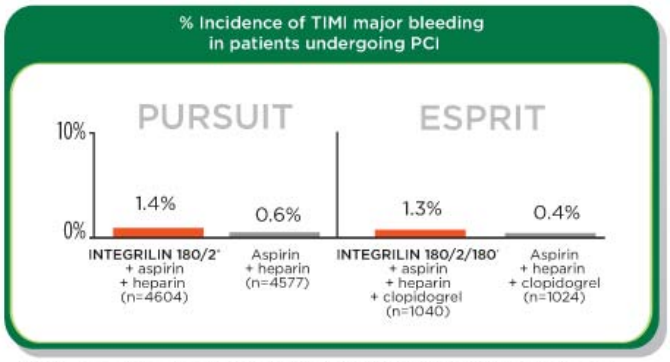
**Note:** The CLEAR PLATELETS study was not designed to provide definitive conclusions about the relation of platelet reactivity to clinical outcomes.

---

Gurbel PA, Bliden KP, Zaman KA, Yoho JA, Hayes KM, Tantry US. Clopidogrel loading with eptifibatide to arrest the reactivity of platelets. Results of the Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study. *Circulation.* 2005;111:1153–1159.

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.

# Incidence of TIMI Major Bleeding in Pivotal Clinical Trials




Major bleeding (TIMI criteria)=a bleeding event resulting in a drop in hemoglobin (Hb) of >5 g/dL.
*180/2=180 mcg/kg IV bolus followed by a 2-mcg/kg/min infusion. The recommended ACT for heparin therapy was between 300 and 350 seconds in patients undergoing PCI.
†180/2/180=180-mcg/kg IV bolus followed by a 2-mcg/kg/min infusion, with a second 180-mcg/kg bolus after the first bolus. The recommended ACT for heparin therapy was between 200 and 300 seconds.

In PURSUIT, the overall incidence of major bleeding was 10.8% with INTEGRILIN® (eptifibatide) vs 9.3% with placebo. The majority of major bleeding occurred during CABG surgery: 8.2% with INTEGRILIN vs 8.2% with placebo.

PURSUIT = **P**latelet Glycoprotein IIb/IIIa in **U**nstable Angina; Receptor **S**uppression **U**sing **I**NTEGRILIN **T**herapy.
ESPRIT = **E**nhanced **S**uppression of the **P**latelet IIb/IIIa **R**eceptor with **I**NTEGRILIN **T**herapy.
TIMI = **T**hrombolysis **I**n **M**yocardial **I**nfarcion.
Fintel DJ, et al. *Clin Cardiol*. 2000;23:V-1–V-12.

INTEGRILIN has a well-established safety profile.[1]

In PURSUIT, the percent incidence of TIMI (**T**hrombolysis **I**n **M**yocardial **I**nfarction) major bleeding in patients undergoing PCI was 1.4% with INTEGRILIN and 0.6% with placebo.
The overall incidence of major bleeding in that trial was 10.8% with INTEGRILIN vs 9.3% with placebo.
The majority of bleeding occurred during CABG surgery: 8.2% with INTEGRILIN vs 8.2% with placebo.*[2]

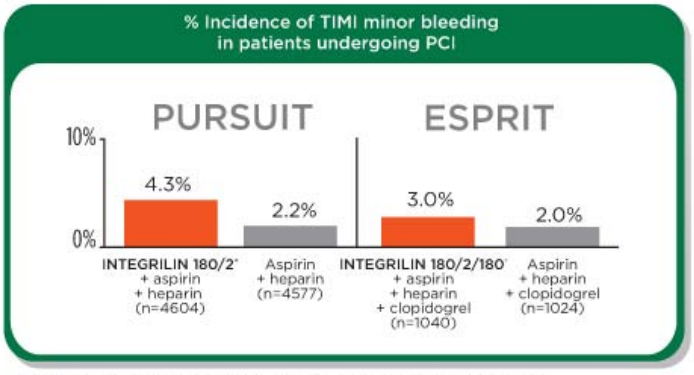
In ESPRIT, the percent incidence of TIMI major bleeding was 1.3% with INTEGRILIN and 0.4% with placebo.[1]

*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 (Hb) greater than 5 g/dL.[1]

1. INTEGRILIN® (eptifibatide) Injection Prescribing Information.
2. Fintel DJ, Ledley GS, eds. Management of patients with non–ST-segment elevation acute coronary syndromes: insights from the PURSUIT trial. *Clin Cardiol.* 2000;23:V-1–V-12.

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.

# Incidence of TIMI Minor Bleeding in Pivotal Clinical Trials




Minor bleeding (TIMI criteria)=a bleeding event resulting in a drop in Hb of >3 g/dL.
*180/2=180 mcg/kg IV bolus followed by a 2-mcg/kg/min infusion. The recommended ACT for heparin therapy was between 300 and 350 seconds in patients undergoing PCI.
†180/2/180=180-mcg/kg IV bolus followed by a 2-mcg/kg/min infusion, with a second 180-mcg/kg bolus after the first bolus. The recommended ACT for heparin therapy was between 200 and 300 seconds.

Fintel DJ, et al. *Clin Cardiol*. 2000;23:V-1–V-12.

In PURSUIT, the percent incidence of TIMI minor bleeding in patients undergoing PCI was 4.3% with INTEGRILIN® and 2.2% with placebo. The overall incidence of minor bleeding in that trial was 13.1% with INTEGRILIN vs 7.6% with placebo.*[1]

In ESPRIT, the percent incidence of TIMI minor bleeding in patients undergoing PCI was 3.0% with INTEGRILIN and 2.0% with placebo.[1,2]

The number of patients requiring transfusions in the PURSUIT trial was 10.4% for placebo, 12.8% for INTEGRILIN 180/1.3,† and 12.8% for INTEGRILIN 180/2.0. The number of patients requiring transfusions in the ESPRIT trial was 1.1% for placebo and 1.5% for INTEGRILIN. The number of patients requiring transfusions in the IMPACT II trial was 5.1% for placebo, 5.5% for INTEGRILIN 135/0.5, and 5.8% for INTEGRILIN 135/0.75.‡[1]

IMPACT II=**I**NTEGRILIN to **M**inimize **P**latelet **A**ggregation and Prevent **C**oronary **T**hrombosis II.

*Bleeding was classified as major or minor by the criteria of the TIMI study group. Minor bleeding events included spontaneous gross hematuria, spontaneous hematemesis, other observed blood loss with a Hb decrease of >3 g/dL, and other Hb decreases that were >4 g/dL but <5 g/dL.

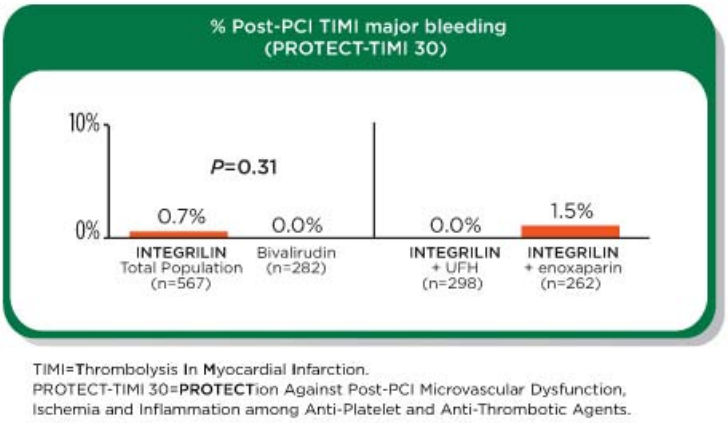
†Administered only until the first interim analysis.

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

1. INTEGRILIN® (eptifibatide) Injection Prescribing Information.
2. Fintel DJ, Ledley GS, eds. Management of patients with non–ST-segment elevation acute coronary syndromes: insights from the PURSUIT trial. *Clin Cardiol.* 2000;23:V-1–V-12.

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.

# Recent Safety Data from the PROTECT-TIMI 30 Trial




TIMI=Thrombolysis In Myocardial Infarction.
PROTECT-TIMI 30=**PROTECT**ion Against Post-PCI Microvascular Dysfunction, Ischemia and Inflammation among Anti-Platelet and Anti-Thrombotic Agents.

Incidence of minor bleeding was: 2.5% with INTEGRILIN® (eptifibatide) vs 0.4% with bivalirudin (*P*=0.027).
Combined incidence of TIMI major and minor bleeding in the overall patient population was 3.2% with INTEGRILIN (n=567).
Gibson CM, et al. In press.

Recent data from the PROTECT-TIMI 30 trial (**PROTECT**ion Against Post-PCI Microvascular Dysfunction, Ischemia and Inflammation Among Anti-Platelet and Anti-Thrombotic Agents) indicate that major TIMI bleeding with INTEGRILIN was not different from that with bivalirudin. The incidence of post-PCI major bleeding was 0.7% with INTEGRILIN (n=567) and 0.0% with bivalirudin (n=282) (*P*=0.31).*

**Study Design**

- PROTECT-TIMI 30 was a randomized open-label, parallel-group, multicenter, international study 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 bivalirduin alone. Patients taking UFH received 50-U/kg bolus with a target ACT of 200 to 250 seconds. All patients received aspirin plus clopidogrel (300 mg) before stenting
- When the dose of INTEGRILIN was reduced for patients with impaired renal function (CrCl <50 mL/min), the incidence of TIMI major bleeding was not significantly different from bivalirudin
- Although the number of patients with CrCl <50 mL/min was small, this study supports the importance of reducing dosing in this population

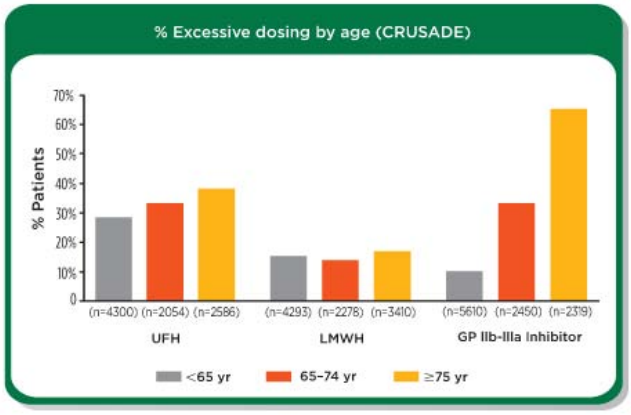
* Bleeding was classified as major or minor by the criteria of the TIMI study group. Major bleeding events consisted of intracranial hemorrhage and other bleeding that led to decreases in hemoglobin greater than 5 g/dL.

---

Gibson CM, Morrow DA, Murphy SA, et al. A randomized trial to evaluate the relative PROTECTion Against Post-PCI Microvascular Dysfunction, Ischemia and Inflammation Among Anti-Platelet and Anti-Thrombotic Agents: the PROTECT-TIMI 30 trial. In press.

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.

## Excessive Dosing of Antithrombotics Increases with Age




From a prospective, observational analysis of 30,136 patients with ACS (UA/NSTEMI) from the CRUSADE National Quality Improvement Initiative Registry.

Alexander KP, et al, for the CRUSADE Investigators. *JAMA*. 2005;294:3108–3116.

Patients with UA/NSTEMI ACS often receive excess doses of antithrombotic therapy, according to the CRUSADE National Quality Improvement Initiative Registry, an ongoing database of high-risk NSTE ACS patients admitted to US hospitals.

The CRUSADE Investigators performed an analysis to investigate the association between dosing and major outcomes for unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and GP IIb-IIIa inhibitors.

The results showed that elderly patients (≥75 years of age) are more likely to receive excess doses of antithrombotic agents than patients <65 years of age. Additional factors increasing the likelihood of excess dosing included renal impairment, female sex, diabetes, prior congestive heart failure, and weight.

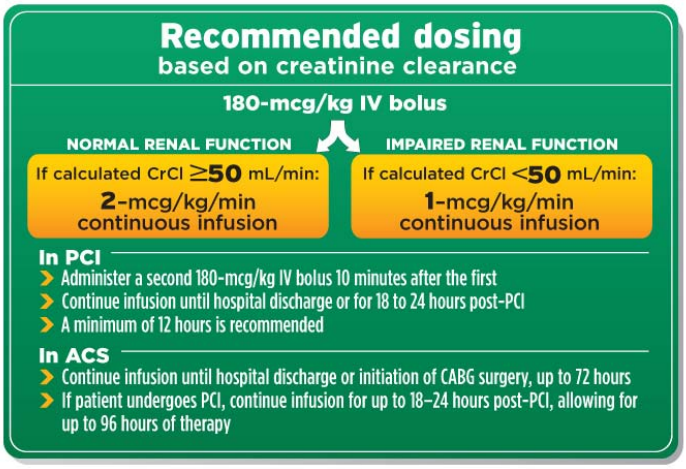
The investigators also found that clinicians often rely on serum creatinine (SCr) as a way to quickly identify renal impairment, even though SCr is a poor indicator of renal function. They concluded that dosing accuracy can be improved if hospitals ensure that estimated creatinine clearance (CrCl) and weight are available at the time of admission.

---

Alexander KP, Chen AY, Roe MT, et al, for the CRUSADE Investigators. Excess dosing of antiplatelet and antithrombin agents in the treatment of non–ST-segment elevation acute coronary syndromes. *JAMA.* 2005;294:3108–3116.

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.

# Appropriate Dosing of INTEGRILIN® (eptifibatide) Is Based on Creatinine Clearance (CrCl)




INTEGRILIN® (eptifibatide) Injection Prescribing Information.

Appropriate dosing of INTEGRILIN is based on creatinine clearance (CrCl), which is influenced by age, gender, weight, and serum creatinine.

**Dosage in acute coronary syndrome (ACS) for adult patients with normal renal function (CrCl ≥50 mL/min):**
The recommended adult dosage of INTEGRILIN in patients with ACS and normal renal function is an intravenous bolus of 180 mcg/kg as soon as possible following diagnosis, followed by a continuous infusion of 2.0 mcg/kg/min until hospital discharge or initiation of CABG surgery, up to 72 hours. If a patient is to undergo PCI while receiving INTEGRILIN, the infusion should be continued up to hospital discharge, or for up to 18 to 24 hours after the procedure, whichever comes first, allowing for up to 96 hours of therapy.

**Dosage in percutaneous coronary intervention (PCI) for adult patients with normal renal function (CrCl ≥50 mL/min):**
The recommended adult dosage of INTEGRILIN in patients with normal renal function is an IV bolus of 180 mcg/kg administered immediately before the initiation of PCI followed by a continuous infusion of 2.0 mcg/kg/min and a second 180-mcg/kg bolus 10 minutes after the first bolus. Infusion should be continued until hospital discharge, or for up to 18 to 24 hours, whichever comes first. A minimum of 12 hours of infusion is recommended.

**In patients with CrCl <50 mL/min, the clearance of eptifibatide is reduced by approximately 50% and steady-state plasma levels approximately are doubled.**

**INTEGRILIN infusion dose should be reduced by half—ie, to 1.0 mcg/kg/min—in patients with moderate to severe renal insufficiency (CrCl <50 mL/min, using the Cockcroft-Gault equation).**

***Please see the following slide for an explanation of the Cockcroft-Gault equation*.**

---

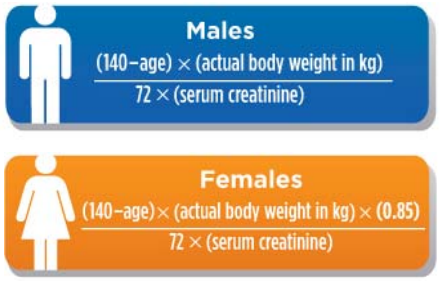
INTEGRILIN® (eptifibatide) Injection Prescribing Information.

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.

## Appropriate Dosing of INTEGRILIN® (eptifibatide) Is Based on Creatinine Clearance (CrCl)

- Infusion dose should be reduced by half in patients with calculated CrCl <50mL/min, which is influenced by:
  - Age
  - Gender
  - Weight
  - Serum creatinine

### Calculating CrCl with Cockcroft-Gault equation




INTEGRILIN® (eptifibatide) Injection Prescribing Information.

This slide shows the Cockcroft-Gault equation, which should be used with actual body weight (in kg) to calculate estimated creatinine clearance (CrCl).[1] A dosing slide rule is available to help make this calculation for patients.

CrCl—which takes into account the patient's age, gender, weight, and serum creatinine—is increasingly being considered a more accurate estimate of renal function (and, hence, of dose adjustment) than serum creatinine alone.[2,3]

In patients with moderate to severe renal insufficiency (CrCl <50 mL/min, using the Cockcroft-Gault equation), the clearance of eptifibatide is reduced by approximately 50% and steady-state plasma levels are approximately doubled.[1]

**Therefore, in patients with calculated CrCl <50 mL/min (using the Cockcroft-Gault equation), INTEGRILIN infusion dose should be reduced by half—ie, to 1.0 mcg/kg/min.**[1]

***Note:*** **In patients with calculated CrCl <50 mL/min who undergo coronary artery bypass graft (CABG) surgery, INTEGRILIN infusion should be discontinued prior to surgery.**[1]

---


1. INTEGRILIN® (eptifibatide) Injection Prescribing Information.
2. Kirtane AJ, Piazza G, Murphy SA, et al. Correlates of bleeding events among moderate to high-risk patients undergoing percutaneous coronary intervention and treated with eptifibatide: observations from PROTECT-TIMI 30. In press.
3. Alexander KP, Chen AY, Roe MT, et al. Excess dosing of antiplatelet and antithrombin agents in the treatment of non–ST-segment elevation acute coronary syndromes. *JAMA.* 2005;294:3108–3116.


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.

# INTEGRILIN® (eptifibatide): Ease of Use


- No reconstitution
- No dilution
- No filter required
- No preparation time required
- No refrigeration required (for up to 2 months of storage at point of use)

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

No preparation time is required with the use of INTEGRILIN, because the product requires no reconstitution, no dilution, and no filter. No refrigeration is required; INTEGRILIN may be stored at room temperature for up to 2 months.

The bolus vial, with a red flip top, is always supplied as a 10-mL vial containing 2 mg of INTEGRILIN per mL. Depending on your hospital formulary, the INTEGRILIN continuous infusion vial is supplied in 1 of 2 configurations: a 100-mL vial containing 0.75 mg of INTEGRILIN per mL, or a 100-mL vial containing 2 mg of INTEGRILIN per mL. Note that the cap and self-contained mechanism for the 0.75-mg/mL infusion vial are yellow; these features for the 2-mg/mL infusion vial are red.

---

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

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.

# INTEGRILIN® (eptifibatide): Bolus Delivery

- Withdraw weight-adjusted bolus dose (determined from dosing chart in Prescribing Information) from a 10-mL bolus vial into a syringe
- Deliver via IV push into IV port closest to the patient

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

The bolus vial contains 10 mL of INTEGRILIN at a concentration of 2 mg/mL. Care should be taken to withdraw the bolus dose from the 2-mg/mL vial. The bolus dose should be withdrawn into a syringe and administered via IV push. The IV infusion dose should follow the bolus dose immediately, without delay.

---

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

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.

## INTEGRILIN® (eptifibatide): Infusion Delivery

- Spike the 100-mL infusion vial with a vented IV infusion set. Care should be taken to center the spike within the circle on the stopper top
- Hang infusion vial from IV pole using the self-contained hanging mechanism
- Administer directly into indwelling IV port or via infusion port of maintenance intravenous solution

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

Hold the 100-mL infusion vial upside down in the palm of your hand and spike with a **vented** infusion set. Care should be taken to spike the vial directly in the center of the circle of the stopper to maintain the integrity of the stopper.

Hang the infusion vial on an IV pole, using the self-contained hanging mechanism. Administer directly from the vial.

Use a **vented** IV infusion set only, as specified in the package insert. Hold the inverted vial on its side at a slight angle while spiking. To maintain the integrity of the stopper, take special care to center the infusion spike within the circle of the stopper top. In the event that the stopper does not have a raised circular center mark, apply the spike as close to the center as possible. If you experience dislodging of the stopper while spiking, the INTEGRILIN vial and the infusion spike must not be used. A new vial and infusion set should be used.

---

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

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.

# GP IIb-IIIa Inhibitors: Administration Requirements

| Administration Requirements | INTEGRILIN® (eptifibatide) Injection | Tirofiban HCl | Abciximab |
|---|---|---|---|
| Filtration required? | No | No | Yes |
| Dilution required? | No | Yes (vial)<br>No (bag) | Yes |
| Refrigeration required? | Can be stored at room temperature for up to 2 months | No | Yes |

INTEGRILIN® (eptifibatide) Injection Prescribing Information.
Aggrastat® (tirofiban hydrochloride injection premixed) Prescribing Information.
ReoPro® (abciximab) Prescribing Information.

Among the GP IIb-IIIa inhibitors, INTEGRILIN has the greatest ease of use. INTEGRILIN requires no filtration and no dilution, and it can be stored at room temperature for up to 2 months.[1]

Aggrastat® (tirofiban HCl) requires no filtration and no refridgeration. Aggrastat in vials (but not bags) must be diluted.[2]

ReoPro® (abciximab) requires filtration, dilution, and refrigeration.[3]

1. INTEGRILIN® (eptifibatide) Injection Prescribing Information.
2. Aggrastat® (tirofiban hydrochloride injection premixed) Prescribing Information.
3. ReoPro® (abciximab) Prescribing Information.

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.

## INTEGRILIN® (eptifibatide): Dosing Compatibilities

- INTEGRILIN may be administered in the same IV line as:
  - Alteplase
  - Atropine
  - Dobutamine
  - Heparin
  - Lidocaine
  - Meperidine
  - Metoprolol
  - Midazolam
  - Morphine
  - Nitroglycerin
  - Verapamil
- INTEGRILIN should not be administered through the same IV line as furosemide
- INTEGRILIN may be administered in the same IV line with 0.9% NaCl or 0.9% NaCl/5% dextrose. With either vehicle, the infusion may also contain up to 60 mEq/L of potassium chloride
- No incompatibilities have been observed with intravenous administration sets
- No compatibility studies have been performed with PVC bags

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

INTEGRILIN may be administered in the same IV line as alteplase, atropine, dobutamine, heparin, lidocaine, meperidine, metoprolol, midazolam, morphine, nitroglycerin, or verapamil.

**INTEGRILIN should *not* be administered through the same intravenous line as furosemide.**

INTEGRILIN may be administered in the same IV line with 0.9% NaCl or 0.9% NaCl/5% dextrose. With either vehicle, the infusion may also contain up to 60 mEq/L of potassium chloride. No incompatibilities have been observed with intravenous administration sets. No compatibility studies have been performed with PVC bags.

---

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

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.

## Summary

- Significant risk reduction before, during, and long after PCI
  - PROTECT — Significantly reduces MI pre-PCI[1]
  - PERFUSE — Improves perfusion to the myocardium[2]
  - PRESERVE — Significant event reduction maintained through 1 year[3]
- Well-established safety profile[1,2,4]
- For patients with UA/NSTEMI, INTEGRILIN® is an ACC/AHA Guidelines IA recommendation[5]
  - Recommended across a spectrum of risk — including high-risk clinical and/or angiographic features[6]

**1.** Fintel DJ, Ledley GS, eds. *Clin Cardiol*. 2000;23:V-1–V-12. **2.** Gibson CM, et al. *Am J Cardiol*. 2001;87:1293–1295. **3.** O'Shea JC, et al. *JAMA*. 2002;287(5):618–621. **4.** INTEGRILIN® (eptifibatide) Injection Prescribing Information. **5.** Braunwald E, et al. ACC/AHA 2002 Guideline Update for UA/NSTEMI. **6.** Smith SC Jr, et al. ACC/AHA/SCAI 2005 Guideline Update for PCI.

- In pivotal clinical trials, INTEGRILIN is associated with a significant reduction in the incidence of ischemic events before, during, and up to 1 year after PCI[1–3]
  - — INTEGRILIN use led to a 67% reduction in the incidence of MI (a reduction from 5.5% to 1.8% when INTEGRILIN was added to aspirin and heparin) in patients prior to undergoing PCI[1]
  - — INTEGRILIN improves perfusion to the myocardium after stent placement[2]
  - — INTEGRILIN leads to significant event reductions that are sustained through 1 year post-treatment[3]
- INTEGRILIN has a well-established safety profile[1–4]
- INTEGRILIN is an ACC/AHA Guidelines IA recommendation
  - — Strong, evidence-based IA recommendation for use in patients with UA/NSTEMI undergoing PCI[5]
  - — Recommended across a spectrum of risk—including high-risk clinical and/or angiographic features[6]


1. Fintel DJ, Ledley GS, eds. Management of patients with non–ST-segment elevation acute coronary syndromes: insights from the PURSUIT Trial. *Clin Cardiol.* 2000;23:V-1–V-12.
2. Gibson CM, Cohen DJ, Cohen EA, et al. Effect of eptifibatide on coronary flow reserve following coronary stent implantation (an ESPRIT substudy). *Am J Cardiol*. 2001;87:1293–1295.
3. O'Shea JC, Buller CE, Cantor WJ, et al. Long-term efficacy of platelet glycoprotein IIb/IIa integrin blockade with eptifibatide in coronary stent intervention. *JAMA.* 2002;287(5):618–621.
4. INTEGRILIN® (eptifibatide) Injection Prescribing Information.
5. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non–ST segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). Available at: http://www.acc.org/clinical/guidelines/unstable/unstable.pdf. Accessed February 21, 2006.
6. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Available at: http://www.americanheart.org/downloadable/heart/1131747703242Summary.pdf. Accessed February 21, 2006.


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.

# INTEGRILIN® (eptifibatide): Contraindications

- 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

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

Treatment with INTEGRILIN 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 stoke within 30 days, or any history of hemorrhagic stroke
- Current of planned administration of another parenternal GP IIb-IIIa inhibitor
- Dependency on renal dialysis
- Known hypersensitivity to any component of the product

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

## INTEGRILIN® (eptifibatide): Precautions and Warnings

- Bleeding is the most common complication encountered during therapy with 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

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

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

---

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

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.

## INTEGRILIN® (eptifibatide): Precautions and Warnings (*cont'd*)

- In patients undergoing PCI, INTEGRILIN is associated with an increase in major 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
- Concomitant treatment with other inhibitors of platelet receptor GP IIb-IIIa to avoid potentially additive pharmacologic events, should be avoided

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

In patients undergoing PCI, patients receiving INTEGRILIN experience an increased incidence of major bleeding compared to those receiving placebo without significant increase in transfusion requirement. 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.** To avoid potentially additive pharmacologic effect, concomitant treatment with **other inhibitors of platelet receptor GP IIb-IIIa** should be avoided.

---

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

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.

## INTEGRILIN® (eptifibatide): Precautions and Warnings (*cont'd*)

- Approximately 50% of INTEGRILIN is cleared in part by the kidney in patients with normal renal function. Plasma concentrations are doubled in patients with an estimated creatinine clearance <50 mL/min (using the Cockcroft-Gault equation). Therefore the infusion dose of INTEGRILIN needs to be reduced to 1 mcg/kg/min in these patients. There has been no clinical experience in patients dependent on dialysis
- Caution should be exercised when administering INTEGRILIN to patients with a platelet count <100,000/mm$^3$

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

**Renal Insufficiency.** Approximately 50% of INTEGRILIN 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 of <50 mL/min (using the Cockcroft-Gault equation). Therefore, the infusion dose should be reduced to 1 mcg/kg/min in such patients. There has been no clinical experience in patients dependent upon dialysis.

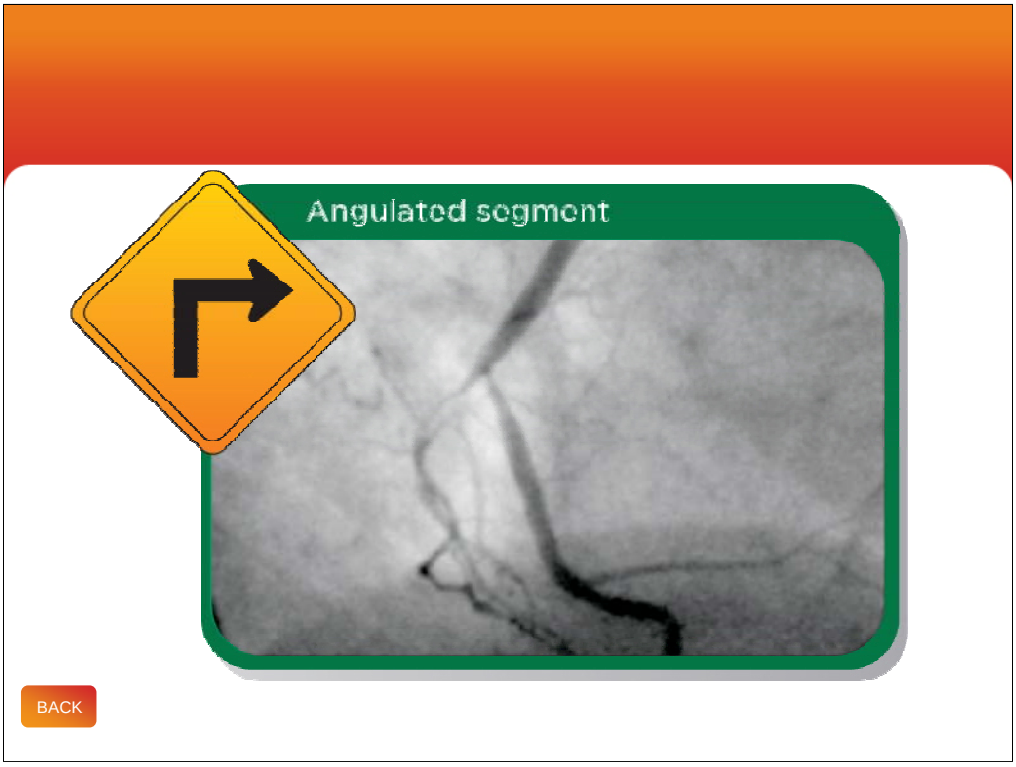
**Platelet Count <100,000/mm$^3$.** Because it is an inhibitor of platelet aggregation, caution should be exercised when administering INTEGRILIN to patients with a platelet count <100,000/mm$^3$; there has been no clinical experience with INTEGRILIN initiated in patients with a platelet count <100,000/mm$^3$.

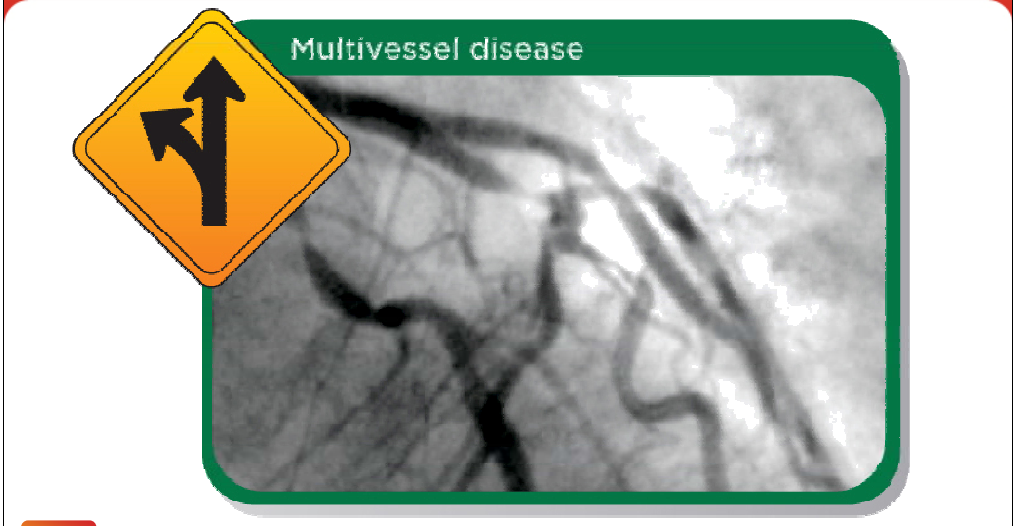
---

INTEGRILIN® (eptifibatide) Injection Prescribing Information.

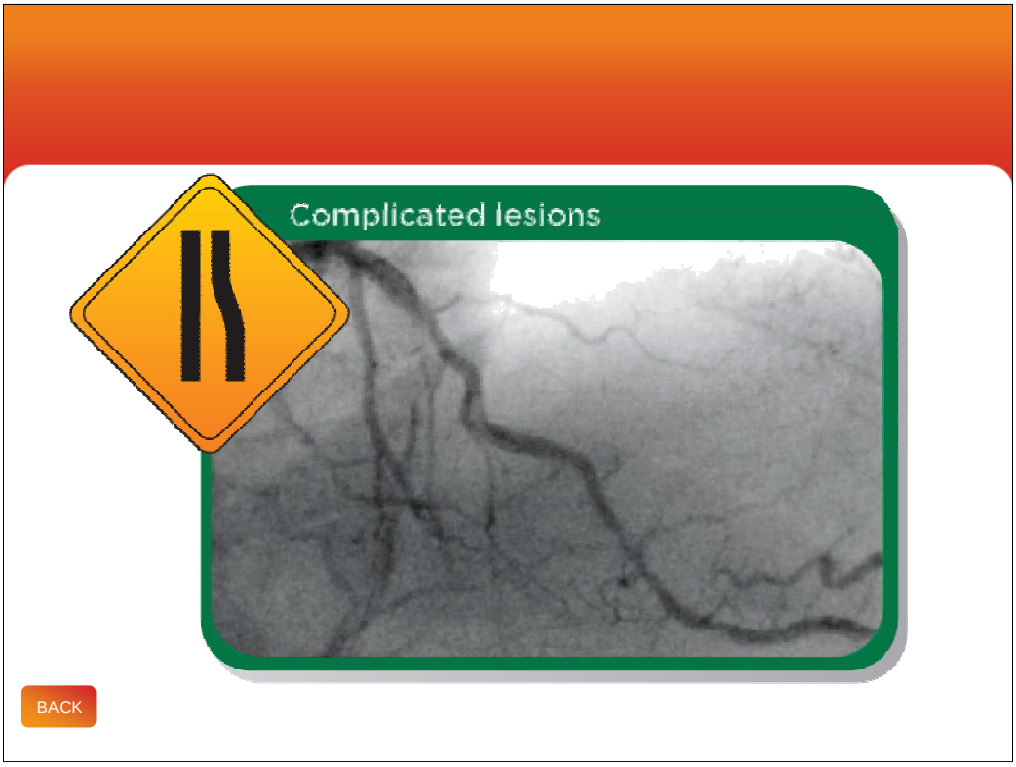
Bleeding is the most common complication encountered during INTEGRILIN therapy. The majority of excess major bleeding events were localized at the femoral artery access site. Oropharyngeal, genitourinary, gastrointestinal, and retroperitoneal bleeding were also seen more commonly with INTEGRILIN compared to placebo.

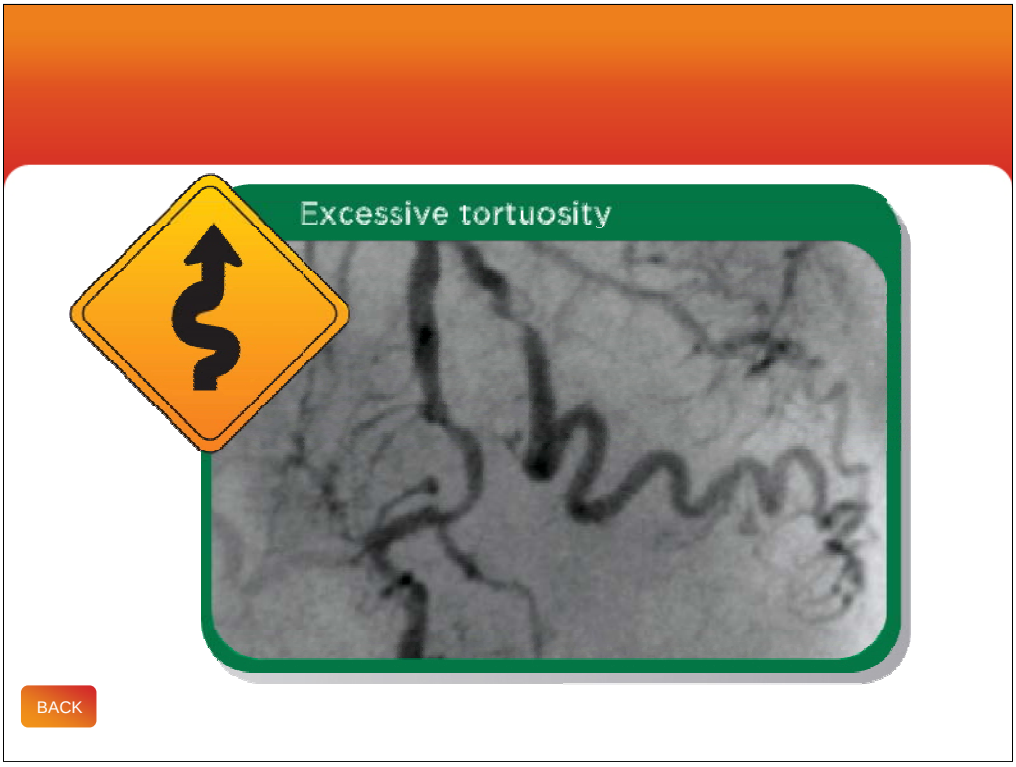
This slide signifies the end of the presentation. The following slides are linked to slide 12.

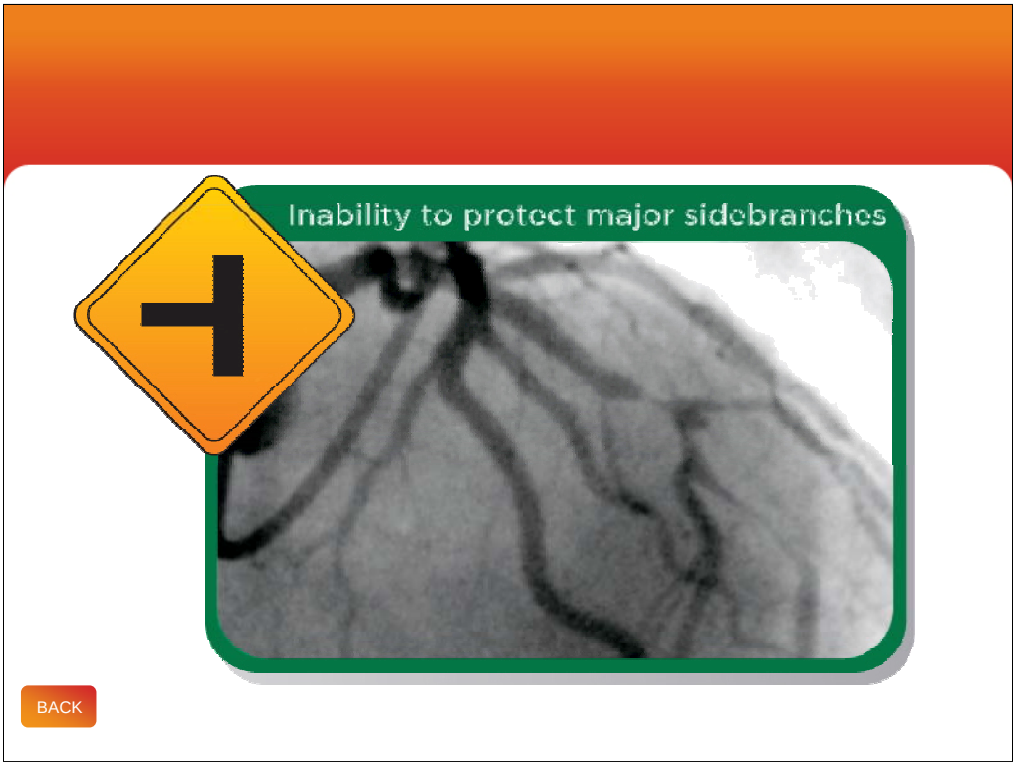

Angulated segment
BACK

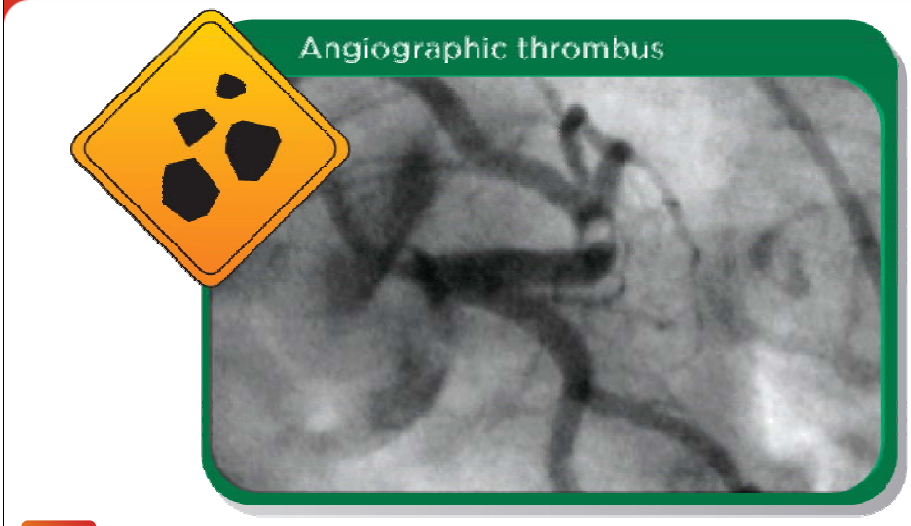



BACK


Complicated lesions
BACK


Excessive tortuosity
BACK


Inability to protect major sidebranches
BACK




BACK