

# Eptifibatide: The evidence for its role in the management of acute coronary syndromes

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**Introduction:** Acute coronary syndromes and non-Q-wave myocardial infarction are often initiated by platelet activation. Eptifibatide is a cyclic heptapeptide and is the third inhibitor of glycoprotein (Gp) IIb/IIIa that has found broad acceptance after the specific antibody abciximab and the nonpeptide tirofiban entered the global market. Gp IIb/IIIa inhibitors act by inhibiting the final common pathway of platelet aggregation, and play an important role in the management of acute coronary syndromes.

**Aims:** This review assesses the evidence for therapeutic value of eptifibatide as a Gp IIb/IIIa inhibitor in patients with acute coronary syndromes.

**Evidence review:** Several large, randomized controlled trials show that eptifibatide as adjunctive therapy to standard care in patients with non-ST segment elevation acute coronary syndrome is associated with a significant reduction in the incidence of death or myocardial infarction. Data are limited regarding the use of eptifibatide in patients with ST segment elevation myocardial infarction. Cost-effectiveness analysis indicates that eptifibatide is associated with a favorable cost-effectiveness ratio relative to standard care. According to US cost-effectiveness analysis about 70% of the acquisition costs of eptifibatide are offset by the reduced medical resource consumption during the first year. Eptifibatide was well tolerated in most of the trials. Bleeding is the most commonly reported adverse event, with most major bleeding episodes occurring at the vascular access site. Major intracranial bleeds, stroke, or profound thrombocytopenia rarely occurred during eptifibatide treatment.

**Place in therapy:** Eptifibatide has gained widespread acceptance as an adjunct to standard anticoagulation therapy in patients with acute coronary syndromes, and may be particularly useful in the management of patients with elevated troponin or undergoing percutaneous coronary interventions.

**Keywords:** eptifibatide, integrilin, myocardial infarction, unstable angina, acute coronary syndrome, percutaneous coronary intervention

## Core evidence place in therapy summary for eptifibatide in the management of acute coronary syndrome

Outcome measure	Evidence	Implication
<b>Patient-oriented evidence</b>		
Improvement in cardiovascular morbidity and mortality	Clear	Lower risk with eptifibatide compared with placebo
Incidence of MI	Clear	Lower risk with eptifibatide compared with placebo

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(Continued)		
Outcome measure	Evidence	Implication
Improvement in quality of life	None	
<b>Disease-oriented evidence</b>		
Urgent target vessel revascularization	Moderate	Lower incidence compared with placebo
Incidence of hemorrhage	Clear	Increased incidence of major and minor bleeding with add-on eptifibatide compared with standard therapy alone
Incidence of thrombocytopenia	Limited	Slightly increased risk of thrombocytopenia with add-on eptifibatide compared with standard therapy alone
Incidence of stroke	Limited	Increased risk of hemorrhagic stroke with add-on eptifibatide compared with standard therapy alone
<b>Economic evidence</b>		
Cost effectiveness compared with other glycoprotein IIb/IIIa inhibitor	Clear	More cost-effective than abciximab in NSTEMI ACS
Cost effectiveness in ACS	Clear	Favorable for eptifibatide as an adjunct to standard care relative to standard care alone
<b>Abbreviations:</b> ACS, acute coronary syndrome; MI, myocardial infarction; NSTEMI ACS, non-ST segment elevation ACS.		

## Scope, aims, and objectives

Eptifibatide (Integrilin®, Millennium, Schering-Plough Corporation) is a cyclic heptapeptide and is the third inhibitor of glycoprotein (Gp) IIb/IIIa that has found broad acceptance as a potent inhibitor of the Gp IIb/IIIa platelet receptor. This review summarizes the development, rationale, and use of this agent in the management of patients with acute coronary syndromes (ACS).

## Methods

English language literature searches were conducted on June 5–10, 2007 in the following databases to date unless otherwise stated. The search strategy was “(myocardial infarction OR unstable angina OR acute coronary syndrome)” AND “(eptifibatide OR integrilin).

- Ovid MEDLINE® 1950 to present with daily update. The following limits were applied: English language and “all

adult (19 plus years)” and “clinical trial, all or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or review.”

- A combined database including Cochrane DSR (Database of Systematic Review), ACP (American College of Physicians) Journal Club, DARE (Database of Abstracts of Reviews of Effects), and CCTR (Cochrane Central Register of Controlled Trials).
- Ovid MEDLINE inprocess and other nonindexed citations June 4, 2007.

Online abstracts from the following congresses were searched using the search strategy “eptifibatide” unless otherwise stated:

- European Society of Cardiology Congress (ESC) 2006/ World Congress of Cardiology (WCC) 2006, ESC Congress 2005 <http://www.escardio.org/knowledge/congresses/abstracts/>.

After removal of duplicates, a total of 160 records were identified. Records were manually reviewed and 59 studies were excluded because the studies were in other diseases or the articles were not investigating the clinical use of eptifibatide in acute coronary syndrome (Table 1).

## Disease overview

ACS has evolved as a useful operational term to refer to any constellation of symptoms that are compatible with acute myocardial ischemia. It encompasses myocardial infarction (MI) (ST segment elevation and depression, Q wave, and non-Q wave) and unstable angina (UA). Disruption of plaques is now considered to be the common pathophysiologic substrate of an ACS. When plaque disruption occurs, a sufficient quantity of thrombogenic substances is exposed (eg, tissue factor), and the coronary artery lumen may become obstructed by a combination of platelet aggregates, fibrin, and red blood cells.

Mural, nonocclusive, white thrombi, consisting predominantly of aggregated platelets, are the cause of cardiac ischemia in most patients (>90%) with UA.<sup>1,2</sup> The pathophysiologic characteristics of non-Q wave MI are similar to those of UA, but this syndrome is accompanied by more severe ischemia and evidence of myocardial necrosis.<sup>3,4</sup> White thrombi also represent an initial stage in the formation of arterial, occlusive red thrombi that produce complete blockage of a coronary artery in acute Q-wave (ST elevation) MI.

The arterial red thrombus is composed of red blood cells enmeshed within a fibrin network. However, it is built on

a white thrombus core that creates regions of blood stasis conducive stated: to fibrin deposition and provides platelet the coagulation cascade.<sup>3-5</sup>

The realization that uncontrolled platelet aggregation could be responsible for thrombosis was appreciated as long ago as 1881, and the concept that thrombosis is the primary cause of ACS has been universally accepted in the last two decades.<sup>4,5</sup> Thus, efforts to prevent ACS have logically focused on development of therapeutic interventions that block platelet aggregation, or coagulation, or both.

Platelet activation occurs through distinct and sometimes redundant physiologic pathways.<sup>4</sup> The ultimate result of the action of these activation signals is platelet aggregation, mediated by cation dependent attachment of divalent fibrinogen molecules to activated platelets. This cross linking of platelets through fibrinogen bridges constitutes the final common pathway in the platelet-mediated thrombus formation. Studies on Glanzmann's thrombasthenia, a rare, inherited, recessive bleeding disorder, provided the first evidence that the integrin Gp IIb/IIIa is the receptor for this crucial fibrinogen-binding event.<sup>6</sup>

The Gp IIb/IIIa complex is the most abundant receptor on the platelet surface. The heterodimeric, ligand-binding Gp IIb/IIIa complexes are not normally exposed in their active forms on the surfaces of the quiescent circulating platelets. However, platelet activation converts Gp IIb/IIIa into competent receptors by means of specific signal transduction pathways,<sup>7</sup> enabling Gp IIb/IIIa to bind fibrinogen and von Willebrand's factor. When two activated platelets with functional Gp IIb/IIIa receptors each bind the same fibrinogen molecule, a fibrinogen bridge is created between the two platelets. Because the surface of each platelet has about 50 000 Gp IIb/IIIa fibrinogen binding sites, numerous activated platelets recruited to the site of vascular injury can rapidly form an occlusive aggregate by means of a dense network of intercellular fibrinogen bridges.<sup>8</sup> This Gp IIb/IIIa-mediated platelet aggregation has served as a target for antiplatelet therapy with Gp IIb/IIIa antagonists.<sup>9</sup>

## Disease burden

ACS are a major cause of emergency medical care and hospitalization in the US. In 2004, the National Center for Health Statistics reported 1 565 000 hospitalizations for primary or secondary diagnosis of an ACS, 669 000 for UA, and 896 000 for MI.

According to the British Heart Foundation (BHF), around 230 000 people in the UK suffer a heart attack each year and in around 30% of heart attacks, the patient dies. Coronary

**Table 1** Evidence base included in the review

Category	Number of records	
	Full papers	Abstracts
Initial search	155	5
Records excluded	59	0
Records included	96	5
Level 1 clinical evidence	3	0
Level 2 clinical evidence	39	
Level 3 clinical evidence	27	
Level 4 clinical evidence	9	
Level 5 clinical evidence	6	
Economic evidence	10	
Case reports	2	

**Notes:** For definitions of levels of evidence, see *Core Evidence* website (<http://www.dovepress.com/core-evidence-journal>).

heart disease is the most common cause of premature death in the UK, causing 105 000 deaths a year.<sup>10</sup>

## Current therapy options

Antiplatelet therapy is the mainstay of therapy in the treatment of patients with ACS that are managed medically or those undergoing percutaneous coronary intervention (PCI) given the importance of platelet activation and aggregation in thrombus formation. Aspirin has been the foundation of antiplatelet therapy and it is recommended as standard therapy in patients with non-ST segment elevation ACS (NSTEMI ACS) with or without PCI as a result of its efficacy and low cost.<sup>11,12</sup> Aspirin is an inhibitor of thromboxane A<sub>2</sub>-induced platelet aggregation and lacks potency and specificity.<sup>13</sup> Lately, aspirin “resistance” has been reported in some patients with cardiovascular disease, with coronary events occurring despite daily aspirin treatment.<sup>14</sup> Thienopyridines (clopidogrel and ticlopidine) are the other class of antiplatelet agents that act through a different mechanism. They inhibit binding of adenosine diphosphate (ADP) to its platelet receptor thereby inhibiting the subsequent ADP-mediated activation of the Gp IIb/IIIa complex, and thus inhibiting platelet aggregation.<sup>12</sup> Clopidogrel reduces the incidence of recurrent ischemic events in patients with ACS and after coronary stenting. However, resistance to clopidogrel has also been reported.<sup>15</sup>

Antithrombotic agents are another class of drugs used in patients with ACS. Unfractionated heparin and low molecular weight heparin (LMWH) are also used in the treatment of patients with non-ST segment elevation ACS and/or those undergoing PCI.

These agents exert their anticoagulant effect by accelerating the rate at which circulating antithrombin (a proteolytic enzyme) inactivates coagulation factors IIa (thrombin), IX, and Xa.<sup>11</sup> Bivalirudin is a peptide that directly inhibits the activity of thrombin and has been used as a substitute for heparin.<sup>11</sup> However, these agents are not antiplatelet agents, but exert their anticoagulant effect on thrombin.

The most groundbreaking development in antiplatelet therapy in recent years has been the development of the intravenous GP IIb/IIIa receptor antagonists (eptifibatide, abciximab [ReoPro® Centocor, Eli Lilly], tirofiban [Aggrastat®, Merck Co Inc]).

Antiplatelet and anticoagulation therapies are essential for the prevention of thromboembolic-induced myocardial ischemia in non-ST elevation ACS and the ischemic complications of PCI. Heparin, direct thrombin inhibitors,

and oral platelet activation inhibitors all provide substantial benefit, but as Gp IIb/IIIa inhibitors block the final common pathway leading to platelet aggregation, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend Gp IIb/IIIa inhibitors as an integral component of care in these patients. The treatment guidelines for the use of GP IIb/IIIa antagonist in UA/ non-ST segment elevation myocardial ischemia (NSTEMI) are shown in Table 2.

Despite the ACC/AHA recommendations, the NRMI-4 (National Registry of Myocardial Infarction 4) and CRU-SADE (Can rapid Risk stratification of Unstable angina patients Suppress ADverse outcomes with early implementation of the ACC/AHA guidelines?) registries observed

**Table 2** American College of Cardiology/American Heart Association guidelines for use of Gp IIb/IIIa antagonists in the management of unstable angina pectoris/non-ST segment elevation myocardial infarction<sup>11</sup>

Class I <sup>a</sup>	A Gp IIb/IIIa antagonist should be administered, in addition to Asp and heparin, to patients in whom catheterization and PCI are planned The Gp IIb/IIIa antagonist may also be administered just prior to PCI <sup>b</sup>
Class IIa <sup>c</sup>	Eptifibatide or tirofiban should be administered, in addition to Asp and LMWH or UFH, to patients with continuing ischemia, elevated troponin levels, or with other high-risk features in whom invasive management is not planned <sup>b</sup> A Gp IIb/IIIa antagonist should be administered to patients already receiving heparin, Asp, and clopidogrel in whom catheterization and PCI are planned The Gp IIb/IIIa antagonist may also be administered just prior to PCI <sup>d</sup>
Class IIb <sup>c</sup>	Eptifibatide or tirofiban should be administered, in addition to Asp and LMWH or UFH, to patients without continuing ischemia who have no other high-risk features and in whom PCI is not planned <sup>b</sup>
Class III <sup>e</sup>	Abciximab administration in patients in whom PCI is not planned <sup>b</sup>

**Notes:** <sup>a</sup>Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.

<sup>b</sup>Evidence from multiple, large, randomized clinical trials.

<sup>c</sup>Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment: IIa=weight of evidence is in favor of usefulness/efficacy; IIb=usefulness/efficacy is less well established by evidence/opinion.

<sup>d</sup>Evidence from a limited number of small randomized trials or from careful analysis of nonrandomized studies or observational registries.

<sup>e</sup>Condition for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

**Abbreviations:** Asp, aspirin; Gp, glycoprotein; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

that only 25%–32% of eligible patients received early Gp IIb/IIIa therapy, despite a 6.3% absolute mortality reduction in NRMI-4<sup>16</sup> and a 2% absolute mortality reduction in CRUSADE.<sup>17</sup>

## Comparison of Gp IIb/IIIa inhibitors

The three available Gp IIb/IIIa inhibitors are abciximab, tirofiban, and eptifibatide. Potentially important differences exist between these agents.

Abciximab, a human-murine chimeric Fab fragment of a monoclonal antibody against the Gp IIb/IIIa receptor, was the first agent of this class to demonstrate clinical effectiveness. The molecular weight of abciximab is 47 615 daltons. Eptifibatide is a synthetic cyclic heptapeptide with a molecular weight of 800 daltons, whereas tirofiban is a nonpeptide with a molecular weight of 495 daltons.

It takes about 4 hours to restoration of normal platelet aggregation after end of infusion of eptifibatide or tirofiban. Abciximab, on the other hand, binds much more avidly to the Gp IIb/IIIa receptor than the other two agents and has a measurable antiplatelet activity for several days (72 hours).<sup>18</sup>

An increased incidence of thrombocytopenia was also observed as a result of treatment with abciximab,<sup>19</sup> including an increase in severe thrombocytopenia (in 0.7% of patients receiving primary treatment, and in 2.2% with retreatment), which suggests that some caution should remain with any readministration of abciximab.

All three agents are available for use in UA/NSTEMI, with abciximab currently approved only in patients undergoing PCI.

## Eptifibatide in combination with other medications

The antiplatelet activity of eptifibatide was the same when coadministered with either unfractionated heparin or the LMWH enoxaparin sodium in ex-vivo studies in healthy volunteers.<sup>20</sup> No difference was found in the antiplatelet activity in patients with ACS undergoing coronary angiography when eptifibatide was used either with enoxaparin or unfractionated heparin.<sup>21</sup> The inhibition of thrombus formation was significantly greater when eptifibatide was coadministered with enoxaparin sodium than with unfractionated heparin [reduction of 75.6% versus 63.9% ( $P = 0.01$ )].

Bivalirudin, a direct thrombin inhibitor, can also be used concomitantly with eptifibatide in patients undergoing PCI.<sup>22</sup> An *ex-vivo* study in patients undergoing PCI showed that during the important periprocedural period (first 8 hours), the

inhibition of platelet aggregation with unfractionated heparin or bivalirudin alone was <80%.<sup>23</sup> Notably, the inhibition of platelet aggregation was significantly ( $P < 0.01$ ) greater with combination therapy (eptifibatide plus unfractionated heparin or bivalirudin) than with either unfractionated heparin or bivalirudin alone at all time points during the infusion.

The addition of eptifibatide therapy in patients with non-ST segment elevation ACS undergoing PCI or elective stenting achieved provides significant with clopidogrel and aspirin alone.<sup>24,25</sup> Inhibition of platelet aggregation was increased at least two-fold when eptifibatide (double bolus dose of 180 mcg/kg then infusion of 2.0 mcg/kg/min) was added to a regimen of clopidogrel 600 mg in the 24 hours after patients were stented.<sup>25</sup> In addition, the release of markers of myocardial necrosis (creatinine kinase MB, troponin I, myoglobin) after PCI was significantly lower when eptifibatide was combined with clopidogrel ( $P < 0.05$ ). Conformationally activated Gp IIb/ IIIa receptor expression after platelet activation with ADP was reduced by 48% with clopidogrel 300 mg plus aspirin therapy, with a further reduction of 80% occurring in patients receiving additional eptifibatide (bolus dose of 180 mcg/kg and then an infusion of 2.0 mcg/kg/min) (both  $P < 0.0001$  versus baseline).<sup>24</sup>

The use of Gp IIb/IIIa in combination with fibrinolytics has potentially several beneficial effects. The combination would attack both the red and the white components of the occlusive thrombus, improve reperfusion and microvascular flow, and might reduce the incidence of postfibrinolytic hemorrhagic stroke if lower dosages of fibrinolytics are used in the combination regimens. Several trials assessing the use of eptifibatide in combination with either full-dose or half-dose fibrinolytics have shown significant improvement in the achievement of thrombolysis in myocardial infarction (TIMI) grade III flow.<sup>26,27</sup> ST segment recovery has also been shown to be more stable and faster with eptifibatide plus a thrombolytic agent.<sup>28</sup>

## Unmet needs

Although eptifibatide and the other two Gp IIb/IIIa inhibitors, by acting on the final common pathway to platelet aggregation, represent an important strategy, there are some potential disadvantages. Attempts to develop new drugs in this class to overcome these disadvantages are ongoing.

## Oral Gp IIb/IIIa inhibition

Because of the benefits of intravenous Gp IIb/IIIa inhibitors, it was hypothesized that prolonged Gp IIb/IIIa inhibition using oral agents might further improve outcomes.



Unfortunately, multiple large trials have failed to show any benefit of this approach.<sup>29,30</sup> In addition, a 35% increase in mortality was seen across the trials.

## Hemorrhage and thrombocytopenia

In a meta analysis of the large placebo-controlled trials, major bleeding was shown to have occurred in 2.4% of patients treated with Gp IIb/IIIa inhibitors versus 1.4% for placebo ( $P < 0.0001$ ).<sup>31</sup>

Thrombocytopenia is an uncommon but important complication of Gp IIb/IIIa inhibitors. For tirofiban in PRISM-PLUS, the rate of severe thrombocytopenia ( $<50\,000$  cells/mm<sup>3</sup>) was 0.5% versus 0.3% for heparin. In the PURSUIT trial, thrombocytopenia ( $<20\,000$  cells/mm<sup>3</sup>) occurred in 0.2% compared with  $<0.1\%$  for heparin. Thrombocytopenia is associated with increased bleeding and, in a smaller proportion of patients, recurrent thrombotic events.<sup>32</sup> This syndrome bears resemblance to heparin-induced thrombocytopenia and indicates a need to monitor platelet count daily during Gp IIb/IIIa infusion.

## Pharmacology of eptifibatide

Eptifibatide is a peptide derived from a protein found in the venom of the southeastern pygmy rattlesnake *Sistrurus miliarius barbouri*.<sup>33,34</sup> It is a cyclic heptapeptide, containing six amino acids and a mercaptopropionyl residue. It belongs to the so called arginine-glycine-aspartate-mimetics and reversibly binds to platelets. It has a modified lysine-glycine-aspartate (KGD) amino acid sequence within its structure, which is similar to the physiologic arginine-glycine-aspartate (RGD) sequence of adhesive ligands, such as von Willebrand's factor and fibronectin, which bind to platelet Gp IIb/IIIa receptors.

In contrast to abciximab, eptifibatide is highly specific for the Gp IIb/IIIa receptor, with a relatively low binding affinity. Since eptifibatide rapidly dissociates from its receptor, normal platelet aggregation is restored approximately 4 hours after discontinuation of an infusion.<sup>34</sup> Eptifibatide is not immunogenic and is safe for repeated administration.<sup>35</sup>

## Dosing regimens

Eptifibatide inhibits platelet aggregation in a dose-dependent manner, as demonstrated by *ex-vivo* studies.<sup>36–38</sup> However variability has been seen in inhibition of platelet aggregation using different *ex-vivo* techniques, which has been attributed to the anticoagulant [sodium citrate or PPACK (D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone)] or the agonist [ADP, thrombin receptor agonist peptide (TRAP)] used.<sup>36,38,39</sup>

When anticoagulants are used that chelate calcium, the affinity of Gp IIb/IIIa for fibrinogen is reduced and the inhibitory effect of the antagonist is overestimated.<sup>40</sup> On the other hand, if TRAP is used as the platelet agonist this might underestimate the *in-vivo* effects of eptifibatide; TRAP causes more platelet degranulation and surface Gp IIb/IIIa expression than ADP, and increases the ability of platelets to aggregate.<sup>38,39</sup> The dosing regimens used in the IMPACT II trial (Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis) were 135 mcg/kg bolus followed by 0.5 mcg/kg/min infusion for 20–24 hours, or 135 mcg/kg bolus plus 0.75 mcg/kg/min infusion for 20–24 hours. Plasma concentrations of eptifibatide during infusion were at the levels expected to inhibit ADP-stimulated platelet aggregation in citrate anticoagulated blood by 70% to 100%. However, as previously discussed, the use of citrate for anticoagulation in platelet aggregation assays leads to a decrease in ionized calcium concentration and the *in-vivo* antiplatelet effects of eptifibatide are therefore overestimated. In PPACK-anticoagulated blood, which is more representative of *in-vivo* physiologic conditions, the degree of inhibition of ADP-induced platelet aggregation by the infusion doses of eptifibatide used in IMPACT II trial would be significantly lower (35%–50%).<sup>41</sup>

Because of the findings of the IMPACT II trial, as well as the realization of caveats inherent in performing platelet aggregation assays in blood anticoagulated with citrate, the specific dosing regimen chosen for the PURSUIT (Platelet Gp IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial was based on an *ex-vivo* platelet aggregation assay that used PPACK as the anticoagulant. The dosing regimen for eptifibatide used in the PURSUIT trial was a bolus of 180 mcg/kg followed by 2.0 mcg/kg/min infusion.<sup>42,43</sup> With this dosing regimen, inhibition of platelet aggregation was 84% at 15 min after the bolus dose and exceeded 90% at steady state. Within 1 hour of the initial eptifibatide bolus, there was a slight loss of inhibition, suggesting a multicompartmental model of distribution of this agent.<sup>36,38</sup> Since PCI is often performed within this timeframe, the ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) trial adopted a regimen that included a second bolus dose (administered within affinity. 10 min of the first) to ensure adequate inhibition of platelet aggregation during PCI.<sup>44</sup>

We have reported a novel dosing regimen for eptifibatide in patients undergoing elective PCI. We used a single high-dose 20 mg (full vial) bolus of eptifibatide, and observed the level of platelet inhibition to be equivalent to the inhibition reported by the TEAM investigators after two weight-adjusted boluses.<sup>45</sup>

The clinical outcomes in this high-dose, single-vial bolus protocol appeared to be at least equivalent to the outcomes observed in the ESPRIT trial, using weight-adjusted bolus plus infusion of eptifibatide in elective stenting.

## Clinical evidence with eptifibatide

### Non-ST segment elevation

#### acute MI (Table 3)

More than 30 000 patients have been enrolled in large, randomized clinical trials comparing inhibition of the platelet Gp IIb/IIIa receptor with standard therapy in patients undergoing percutaneous coronary revascularization and those with ACS who do not have ST segment elevation.<sup>46</sup> Although the magnitude of benefit has varied, there has consistently been a reduction in the incidence of death and myocardial infarction and the need for revascularization.

In the PURSUIT trial<sup>43</sup> a total of 10 948 patients were enrolled. This landmark multicenter trial found that eptifibatide reduced the incidence of death or nonfatal MI at 30 days. The absolute 1.5% reduction was achieved early during the drug infusion and persisted through 30 days. Coronary intervention was performed at the discretion of the treating physician and thus not subject to randomization. The use of eptifibatide was associated with increased bleeding and a more frequent need for transfusions compared with placebo. Although we observed a beneficial effect of eptifibatide in men, the results were less clear in women. The benefit of eptifibatide was evident at 96 hours and the maintenance of this benefit without attenuation persisted up to 30 days.

The INTERACT trial<sup>47</sup> randomized 746 patients to evaluate the efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non-ST segment elevation ACS receiving eptifibatide and aspirin. At 30 days, there was a 44% relative reduction in death or MI in the enoxaparin-treated group (5% versus 9%,  $P = 0.031$ ). Limitations of the study include the fact that it was an open-label study and that the time to coronary revascularization was 101 hours.

The 9 500-patient EARLY ACS trial,<sup>48</sup> which was due to complete in July 2008, evaluates the utility of early eptifibatide administered as a double bolus plus infusion compared with initial placebo therapy with provisional eptifibatide begun just before PCI in patients with non-ST segment elevation ACS in whom an invasive approach is planned no sooner than the next calendar day. This study will also provide important information regarding the interaction between biomarkers, genetics, prognosis, and the magnitude of benefit from early use of eptifibatide in patients with non-ST segment elevation ACS.

In summary, in the large landmark PURSUIT trial, the moderate absolute reduction of 1.5% in the incidence of death or nonfatal MI was achieved with eptifibatide in a real-life setting and in a broad population of patients. PURSUIT represents the largest study of Gp IIb/IIIa inhibition to date, and is consistent with the overall reduction of death and MI observed with this class of drugs. Among high-risk patients with non-ST segment elevation ACS, treatment with the LMWH enoxaparin in combination with eptifibatide was associated with a lower rate of major bleeding at 96 hours, as well as lower rates of ischemia during and immediately following treatment and lower rates of death or MI at 30 days.

### ST segment elevation MI (Table 4)

Studies have investigated the use of eptifibatide as combination therapy with fibrinolytics or prior to primary PCI in the emergency room.

Reperfusion in the infarct-related artery is a main predictor of survival after thrombolysis for acute MI.<sup>36</sup> Accelerated alteplase restores normal perfusion but only in approximately 50% of cases,<sup>27,49</sup> perhaps even less at the tissue level.<sup>26</sup> Only modest success has come from pharmacologic and other approaches to improving the incidence and speed of reperfusion.

The IMPACT-AMI Investigators<sup>36</sup> demonstrated in a small randomized, placebo-controlled, dose-ranging trial that the incidence and speed of reperfusion can be enhanced when a potent Gp IIb/IIIa inhibitor is combined with accelerated alteplase, aspirin, and intravenous heparin. One hundred and thirty-two patients in a 2:1 ratio received a bolus and continuous infusion of one of six eptifibatide doses or placebo. Another 48 patients were randomized in a 3:1 double-blind fashion to receive the highest eptifibatide dose from the first phase or placebo. All patients received accelerated alteplase, aspirin, and intravenous heparin infusion; all but two groups also received an intravenous heparin bolus. The highest eptifibatide dose group from the nonrandomized phase and the randomized patients were pooled for analysis and compared with placebo-treated patients. The primary endpoint was TIMI grade III flow at 90-min angiography. Secondary endpoints were time to ST segment recovery, an inhospital composite endpoint (death, reinfarction, stroke, revascularization procedures, new heart failure, or pulmonary edema), and bleeding variables.

The groups receiving the largest dose of eptifibatide had more complete reperfusion (TIMI grade III flow, 66% versus 39% for placebo-treated patients;  $P = 0.006$ ) and a shorter

**Table 3** Studies with eptifibatide in patients with non-ST segment elevation MI

Study name	Inclusion criteria	Patients (n)	Primary endpoint (combined)	Results	
				Primary endpoint	Hemorrhage
PURSUIT	Non-ST elevation acute coronary syndromes	10 948	All-cause death, nonfatal MI (30 days)	Eptifibatide 14.2% vs placebo 15.7% ( $P < 0.05$ )	Eptifibatide 10.6% vs placebo 9.1% ( $P < 0.005$ ) <sup>a</sup>
INTERACT	Non-ST elevation acute coronary syndromes	746 All patients received aspirin and eptifibatide, plus either enoxaparin or UFH	Major bleed by 96 h and recurrent ischemia by 96 h	Major bleed at 96 h reduced with enoxaparin vs UFH but minor bleed increased (30.3% vs 20.8%; $P = 0.003$ )	
IMPACT II	Elective, urgent, or emergency PCI	4010	All-cause death, nonfatal MI, urgent or emergency revascularization (30 days)	Eptifibatide 135/0.5 <sup>b</sup> 9.2% vs placebo 11.4% (ns) Eptifibatide 135/0.75 <sup>c</sup> 9.9% vs placebo 11.4% (ns)	Eptifibatide 135/0.5 <sup>b</sup> 5.1% vs placebo 4.8% (ns) Eptifibatide 135/0.75 <sup>c</sup> 5.2% vs placebo 4.8% (ns)

**Notes:** <sup>a</sup>Severe bleeding (TIMI criteria).

<sup>b</sup>Eptifibatide 135 mcg/kg bolus followed by 0.5 mcg/kg/min infusion for 20–24 h.

<sup>c</sup>Eptifibatide 135 mcg/kg bolus followed by 0.75 mcg/kg/min infusion for 20–24 h.

**Abbreviations:** h, hours; MI, myocardial infarction; ns, not significant; PCI, percutaneous coronary intervention; TIMI, thrombolysis in MI; UFH, unfractionated heparin.

median time to ST segment recovery (65 versus 116 min for placebo;  $P = 0.05$ ). The groups had similar rates of the composite endpoint (43% with eptifibatide versus 42% with placebo) and severe bleeding (4% versus 5%). However, the patients enrolled in the trial were relatively low risk. Elderly patients and those with cardiogenic shock were excluded, which may have resulted in some selection bias. Secondly, this was a small study of 180 patients, of whom only 51 received the largest dose of eptifibatide. Thus, interpretations should be made with caution.

In the INTRO-AMI trial<sup>26</sup> patients were enrolled in a dose-finding (phase a,  $n = 344$ ) followed by a dose-confirmation (phase b,  $n = 305$ ) protocol. All patients received aspirin and weight-adjusted heparin and underwent angiography at 60 and 90 min. In phase a, eptifibatide in a single or double bolus (30 min apart) of 180, 180/90, or 180/180 mcg/kg followed by an infusion of 1.33 or 2.0 mcg/kg min was sequentially added to alteplase 25 or 50 mg. In phase b, patients were randomized to: double-bolus eptifibatide 180/90 mcg/kg (30 min apart) and 1.33 mg/kg/min infusion, with alteplase 50 mg (group I); 180/90 mcg/kg (10 min apart) and 2.0 mg/kg/min, with alteplase 50 mg (group II); or full-dose, weight-adjusted alteplase (group III).

In phase a, the best rate of TIMI flow grade III was achieved using 180/90/1.33 mcg/kg per min eptifibatide with 50 mg alteplase: 65% and 78% at 60 and 90 min, respectively.

In phase b, the incidence of TIMI flow grade III at 60 min was 42%, 56%, and 40%, for groups I through III, respectively ( $P = 0.04$ , group II versus group III). The median corrected TIMI frame count was 38, 33, and 50, respectively ( $P = 0.02$ ). TIMI major bleeding was reported in 8%, 11%, and 6%, respectively; intracranial hemorrhage occurred in 1%, 3%, and 2% of patients ( $P > 0.5$  for both). The incidences of death (4%, 5%, and 7%), reinfarction, or revascularization at 30 days were similar among the three treatment groups.

This study showed that double-bolus (within a 10-min interval) and high-dose infusion of eptifibatide combined with half-dose alteplase is superior to standard-dose alteplase alone in achieving reperfusion of the infarct-related artery 60 min after initiation of therapy. A 16% absolute difference in TIMI flow grade III was achieved without a significant bleeding events, although a higher nominal rate of intracranial hemorrhage was observed in the patients with the highest rate of reperfusion. More than 75% of the episodes of major bleeding were associated with the catheterization access site and did not affect clinical outcome. Like any intervention,



**Table 4** Studies with eptifibatide in patients with ST segment elevation myocardial infarction (STEMI)

Name of study	Inclusion criteria	Patients (n)	Primary endpoint (combined)	Results	Primary end point	Hemorrhage
INTAMI	STEMI	102	TIMI III patency prior to PCI	Eptifibatide 14.2% vs placebo 15.7% ( $P < 0.05$ )	Eptifibatide 10.6% vs placebo 9.1% ( $P < 0.05$ ) <sup>a</sup>	
INTEGRITI	STEMI	438	TIMI grade III flow in the infarct-related artery at 60 min	Arterial patency was highest for eptifibatide 180/2/180 <sup>b</sup> plus half-dose TNK (96%, $P = 0.02$ vs eptifibatide 180/2/90 <sup>c</sup> plus half-dose TNK) Combination therapy tended to achieve more TIMI III flow, patency, and ST segment resolution compared with TNK monotherapy	Trend towards increased rates of major hemorrhage (7.6% vs 2.5%; $P = 0.14$ ) and transfusions (13.4% vs 4.2%; $P = 0.02$ ) with combination therapy	
TITAN-TIMI 34	STEMI undergoing primary PCI	316	CTFC	CTFC faster in earlier administration group vs CCL administration (77.5 vs 84.3; $P = 0.049$ )	TIMI major and minor bleed rate similar between groups (6.9% vs 7.8%, ns)	
IMPACT-AMI	STEMI	180	TIMI grade III flow at 90 min	Highest dose eptifibatide + tPA group had TIMI grade III flow 66% versus 39% for placebo; $P = 0.006$	Severe bleed rate similar (4% vs 5%, ns)	

**Notes:** <sup>a</sup>Severe bleeding (TIMI Criteria).<sup>b</sup>Eptifibatide 180 mcg/kg bolus followed by 2 mcg/kg/min infusion then a second 180 mcg/kg bolus 10 min later.<sup>c</sup>Eptifibatide 180 mcg/kg bolus followed by 2 mcg/kg/min infusion then a second 90 mcg/kg bolus 10 min later.**Abbreviations:** CCL, cardiac catheterization laboratory; CTFC, corrected TIMI frame count; ns, not significant; PCI, percutaneous coronary intervention; TIMI, thrombolysis in MI; TNK, tenecteplase; tPA, alteplase.

the clinical utility of this strategy hinges on the trade off between safety and efficacy.

In the INTEGRITI trial,<sup>27</sup> combination reperfusion therapy with eptifibatide and reduced dose tenecteplase for ST segment elevation MI (STEMI) TIMI grade III flow rates were similar across groups (64%–68%). Arterial patency was highest for a regimen of eptifibatide 180 mcg/kg bolus followed by 2.0 mcg/kg/min infusion, then a second 180 mcg/kg bolus 10 min later plus half-dose tenecteplase (eptifibatide 180/2/180 plus half-dose tenecteplase; 96% versus 84% with eptifibatide 180/2/90 plus half-dose tenecteplase;  $P = 0.02$ ). In dose confirmation, the combination of eptifibatide 180/2/180 plus half-dose tenecteplase compared with tenecteplase monotherapy tended to achieve TIMI grade III flow in slightly more patients (59% versus 49%;  $P = 0.15$ ), slightly greater arterial patency (85% versus 77%;  $P = 0.17$ ), and ST segment resolution slightly more frequently (median 71% versus 61%;  $P = 0.08$ ) but was associated with a somewhat greater incidence of major hemorrhage (7.6% versus 2.5%;  $P = 0.14$ ) and requirement for transfusions (13.4% versus 4.2%;  $P = 0.02$ ). Intracranial hemorrhage occurred in 1.0%, 0.6%, and 1.7% of patients treated with any combination, eptifibatide 180/2/180 and half-dose tenecteplase, and tenecteplase monotherapy, respectively. This randomized controlled, open-label, phase II angiographic trial therefore tended to suggest that double-bolus eptifibatide 180/2/180 plus half-dose tenecteplase may improve angiographic flow and ST segment resolution compared with tenecteplase monotherapy but may be associated with more transfusions and noncerebral bleeding.

In another trial<sup>50</sup> the effect of emergency room administration of eptifibatide before primary angioplasty for STEMI on baseline coronary flow and procedure outcomes was assessed. The results of this study show that for patients undergoing primary angioplasty for STEMI, administering eptifibatide early after presentation and before arrival in the cardiac catheterization laboratory provides partial reperfusion and may decrease procedure complexity. Of 30 patients who received eptifibatide administered as a double bolus of 180 mcg/kg with the initial bolus given  $51 \pm 27$  min before baseline angiography, 17 (56.7%) had TIMI grade II or III flow. In addition, the time from baseline angiography to first balloon inflation was less for these patients, including those who did not achieve partial reperfusion. This advantage was offset by a delay in the time from emergency room presentation to baseline angiography, such that time from presentation to balloon inflation was similar in the two groups. The total procedure time and length of stent required for those lesions

in which stents were implanted were significantly less for patients who received early eptifibatide treatment. Although in a relatively small number of patients, these findings suggest that in addition to improved flow characteristics, early administration of eptifibatide may modify the thrombotic lesion, facilitating the performance of angioplasty.

The INTAMI study<sup>51</sup> was a small randomized trial that assigned 102 patients with STEMI < 12 hours to primary percutaneous intervention with early eptifibatide given in the emergency room or optional eptifibatide at the time of PCI (late or no). The primary endpoint was the patency of the infarct vessel before PCI. Patients in the early group received their first eptifibatide bolus a mean of 45 min before angiography. TIMI grade III patency before PCI was observed in 34% in the early group and 10% in late or no group ( $P = 0.01$ ). The incidence of complete ST resolution 1 hour after PCI was similar at 61% in the early group and 66% in the late or no group. Furthermore, there were no significant differences in the rates of TIMI grade III flow after PCI, death, reinfarction, stroke, and major bleeding complications until day 30. However, the trial was not powered to detect differences in clinical endpoints.

TITAN-TIMI 34<sup>52</sup> was a randomized, phase IV, open-label, multicenter trial to evaluate the angiographic and clinical efficacy of early initiation of eptifibatide in patients intended to undergo primary PCI for acute STEMI. Patients were randomized 1:1 in blocks of 10 at each study site to receive eptifibatide (180/2/180) to be started either immediately in the emergency department (ED) or other triage unit (early ED administration) ( $n = 174$ ) versus initiation in the cardiac catheterization laboratory (CCL) ( $n = 142$ ) after diagnostic catheterization (late CCL administration). The primary endpoint of corrected TIMI frame count on diagnostic angiography was lower (ie, faster) in the ED group (77.5 frames versus 84.3 frames;  $P = 0.049$ ). TIMI grade II or III flow was higher in the ED group (46.2% versus 36.6%;  $P = 0.087$ ), while the rate of TIMI grade III flow was 24.0% in the ED group and 19.0% in the CCL group ( $P = 0.29$ ). TIMI myocardial perfusion grade III was present more frequently in the ED group (24.3% versus 14.2%;  $P = 0.026$ ). There was no difference in post-PCI TIMI frame count (20 versus 22 frames;  $P = 0.14$ ), TIMI flow grade (87% versus 89%;  $P =$  not significant), or TIMI myocardial perfusion grade (37% versus 37%;  $P =$  not significant). However, full angiographic perfusion score (APS), which integrates pre-PCI and post-PCI epicardial and myocardial perfusion, trended better in the ED group (APS of 10–12, 21.1% versus 12.5%;  $P = 0.059$ ).

Hence a strategy of early initiation of eptifibatide in the ED before primary PCI for STEMI yields superior pre-PCI TIMI frame counts, reflecting epicardial flow and superior TIMI myocardial perfusion compared with a strategy of initiating eptifibatide in the CCL.

In summary, there are limited trials using eptifibatide in early invasive strategy of management of STEMI. Most of the early trials used abciximab and tirofiban. The available data at best suggest a superior TIMI flow grade as well as perfusion grade with the use of eptifibatide at the cost of increased hemorrhagic complications.

## Economic evidence

In the PRICE study<sup>53</sup> a prospective economic analysis showed that median total in-hospital costs (1999/2000 year of costing) were significantly lower in eptifibatide than in abciximab recipients (\$US7207 versus \$US8268 per patient;  $P = 0.009$ ). The between-group difference in cost was largely attributable to the higher acquisition costs within the abciximab-treated group. In-hospital charges, 30-day total costs, and 30-day total charges were also significantly ( $P < 0.01$ ) lower with eptifibatide than abciximab.

Retrospective analyses<sup>54–56</sup> that compared eptifibatide with abciximab as adjunctive therapy in patients undergoing PCI have generally indicated that eptifibatide was associated with lower acquisition costs and similar or lower total medical costs or charges per patient; clinical outcomes were similar with the two agents. These studies varied in methodologies and year of costing, but were all conducted in the US; several of these studies also included tirofiban as a comparator. In the largest of these studies (data from 32,529 patients reviewed), the incremental cost-effectiveness ratios of eptifibatide, abciximab, and tirofiban compared with standard treatment were \$US21,731, \$US14,515, and \$US163,286 per life-year gained, respectively (year of costing 2000/2001).

Several cost-effectiveness analyses used prospectively collected data from the PURSUIT trial and modeled survival projections using similar methods. These analyses, conducted in the US, Canada, and Western Europe, also showed favorable results (\$US3761–\$US18 774 per life-year gained; various years of costing).<sup>57</sup> Cost-utility ratios reported in US analyses varied somewhat, but remained  $< \$US20\ 000$  per quality-adjusted life-year gained (1996 values) when clinical efficacy data were derived from the US cohort of PURSUIT.

Significant clinical benefits have been demonstrated with eptifibatide as adjunctive therapy in patients undergoing selective PCI with stent implantation in the ESPRIT

trial and in patients with ACS in the PURSUIT trial. Pharmacoeconomic analyses using data from these trials have demonstrated favorable cost-effectiveness ratios for both indications in various countries.<sup>57</sup> ESPRIT-based results from the limited number of available economic analyses are particularly favorable.<sup>57</sup> In US economic analyses using ESPRIT trial data, approximately 40% and 70% of the acquisition cost of eptifibatide was offset by reduced medical resource consumption during the initial hospitalization period and over a 1-year period, respectively. Eptifibatide was associated with a favorable cost-effectiveness ratio of \$US1407 (year 2000 values) per life-year gained in a retrospective US cost-effectiveness analysis that incorporated data from the ESPRIT trial and modeled life expectancy using a large cardiovascular database.

The cost effectiveness of eptifibatide in ACS may be further improved by targeting the drug for patients in whom catheterization and PCI are planned, although further analyses are required to confirm this.

## Resource utilization

In the ESPRIT trial the estimated in-hospital costs for each patient on the basis of hospital resource consumption (procedure duration, number of stents received, length of stay), occurrence of adverse outcomes (death, periprocedural acute MI, repeat PCI, in-hospital coronary artery bypass graft surgery, major bleeding complications), and treatment received<sup>58</sup> were estimated on the basis of measured resource consumption, using a published regression model. Costs associated with length of stay and adverse outcomes were estimated from a second regression model, which was based on measured hospital costs for 3241 patients who underwent PCI between 1996 and 1999 at 89 US hospitals (model  $R^2 = 0.69$ ). Reflecting the observed reductions in stent use and procedure duration, initial procedural costs were \$US151 lower per patient for patients treated with eptifibatide compared with placebo. In addition, hospital costs related to treatment of periprocedural ischemic complications were \$US61 lower per patient for the eptifibatide group. However, there were no significant differences in costs related to the length of stay or treatment of vascular complications. As a result, mean total initial hospital costs (excluding eptifibatide) were \$US185 lower per patient for the eptifibatide group compared with placebo (\$US10,226 versus \$US10,412;  $P = 0.15$ ). When the cost of study drug was included, mean total initial hospital costs were increased by \$US292 per patient with eptifibatide compared with placebo (\$US10722 versus \$US10,430;  $P < 0.001$ ).

However, a US cost-effectiveness analysis (year of costing 2000) indicated that eptifibatide was associated with a favorable cost-effectiveness ratio of \$US1407 per life-year gained relative to standard care.<sup>57</sup> Approximately 70% of the acquisition costs of eptifibatide were offset by the reduced medical resource consumption during the first year.

## Patient group/population

Eptifibatide has been studied in different patient populations. The efficacy of low dose eptifibatide was first evaluated in a small number of patients ( $n = 150$ ) in the IMPACT-I trial.<sup>59</sup> The patients in this study were undergoing low- and high-risk coronary intervention. The data from the larger IMPACT-II trial provided the initial supporting evidence for the efficacy of a low-dose regimen (bolus of 135 mcg/kg then a continuous intravenous infusion of 0.5 or 0.75 mcg/kg/min) of this agent in this indication.<sup>46</sup> There was no significant difference between eptifibatide and placebo recipients in the incidence of the primary composite endpoint of death, MI, or urgent target vessel revascularization (UTVR) at 30 days in this trial.

Based on these data and results from other pharmacodynamic studies, the ESPRIT trial<sup>44</sup> investigated the efficacy of an eptifibatide dosage that was three- to four-fold higher than that used in the IMPACT-II trial. The researchers from the ESPRIT trial concluded that as adjunctive treatment in patients with low- to moderate-risk coronary artery disease undergoing PCI with stent placement, eptifibatide achieved significant reductions in ischemic complications and was better than a strategy of reserving treatment for the bailout situation. The risk of the primary endpoint (a composite of death, MI, UTVR, and bailout to open-label eptifibatide within 48 hours) was significantly reduced with eptifibatide versus placebo [risk ratio (RR) 0.63; 95% confidence interval (CI) 0.47, 0.84]. This benefit associated with eptifibatide occurred across different subgroups regardless of sex, presence of diabetes, or other comorbid clinical conditions. In addition, eptifibatide recipients had a significantly lower risk of secondary endpoint (death, MI, or UTVR at 30 days) (RR 0.65; 95% CI 0.47, 0.87).

Subsequent follow-up analyses of these trials<sup>60,61</sup> indicated that adjuvant eptifibatide therapy provides long-term benefit. In addition to the lower combined incidence of death, MI, or UTVR in eptifibatide than in placebo recipients at 48 hours and 30 days, the incidence was also lower with eptifibatide at 6 and 12 months.

Eptifibatide has also been studied in various patient populations with ACS. In the PURSUIT trial 1228 patients were

enrolled who had NSTEMI and underwent PCI during the first 72 hours of the trial.<sup>62</sup> The incidence of the composite endpoint death or MI within 30 days was significantly lower in eptifibatide than in placebo recipients (11.6% versus 16.7%;  $P = 0.01$ ). The between-group difference was not significant in the other 8233 patients who did not undergo early PCI (14.6% versus 15.6%). In another retrospective analysis of PURSUIT trial data of patients randomized in the US (who received earlier intervention strategies than those from other regions) ( $n = 4035$ ), the reduction in the 30-day risk of the composite endpoint significantly favored eptifibatide versus placebo recipients ( $P < 0.05$ ), both in patients who underwent an early PCI and in those who did not (relative risk reductions of 33% and 19%).<sup>63</sup>

Data are limited regarding the use of eptifibatide in patients with STEMI. Studies have investigated the use of eptifibatide prior to primary PCI in the emergency room<sup>50</sup> or as combination therapy with fibrinolytics<sup>26,27,36,49</sup> in patients with STEMI. Eptifibatide is not currently approved in these indications.

The early administration of eptifibatide in the emergency room before primary PCI in patients with STEMI resulted in a significantly higher rate of partial or complete reperfusion than standard treatment.<sup>49</sup> The effect of combination therapy with eptifibatide plus a fibrinolytic on surrogate markers of epicardial and myocardial reperfusion in patients with STEMI has been examined in phase II clinical trials<sup>26,27,36,49</sup> and a meta analysis.<sup>28</sup> The primary endpoint in these trials was generally the proportion of patients with TIMI grade III flow assessed by angiography. All patients in these studies received aspirin and unfractionated heparin. The phase III ADVANCE-MI trial was initiated to evaluate the efficacy of eptifibatide alone or in combination with reduced-dose tenecteplase in patients with STEMI who were to undergo PCI within 4 hours. The primary endpoint of this trial was an improvement in patient survival and a reduction in the rate of congestive heart failure, but the trial was terminated early. In two trials [INTRO-AMI<sup>26</sup> and IMPACT-AMI]<sup>36</sup> significantly more patients receiving eptifibatide in combination with alteplase, compared with those receiving alteplase alone, experienced TIMI grade III flow. However, in the INTEGRITI trial,<sup>27</sup> adding eptifibatide to tenecteplase or streptokinase<sup>49</sup> did not significantly improve this outcome. The proportion of patients with TIMI grade II or III flow was also greater with eptifibatide plus a fibrinolytic than with a fibrinolytic alone in two trials. However, in the latter trial<sup>49</sup> the addition of eptifibatide to full-dose streptokinase was associated with an increase in bleeding.

Patients with prior coronary artery bypass grafts (CABG) have a worse prognosis than those without a history of CABG; however, the effect on the incidence of death or MI at 30 days with eptifibatide versus placebo was similar in patients with prior CABG and in patients without prior CABG (14.1% versus 15.5%; unadjusted heart rate 0.89; 95% CI 0.80, 0.99).<sup>64</sup> In patients with non-ST segment elevation ACS who underwent in-hospital CABG ( $n = 1558$ ), eptifibatide treatment resulted in a significantly lower incidence of death or MI at 7 days than placebo (17.4% versus 22.3%;  $P = 0.017$ ) that persisted through to the 6-month follow-up (27.6% versus 32.7%;  $P = 0.029$ ).<sup>65</sup>

## Dosage, administration, and formulation

Eptifibatide is indicated in the US in patients with UA pectoris and NSTEMI. Eptifibatide is indicated for the treatment of patients undergoing PCI, including those undergoing intracoronary stenting. It is also indicated for patients with angina and NSTEMI that are managed medically. In Europe, eptifibatide is indicated for the prevention of early MI in patients presenting with UA pectoris or non-Q wave MI and with electrocardiogram changes and/or elevated cardiac enzymes. Patients at high risk of developing MI within the first 3–4 days after onset of acute angina symptoms, including those likely to undergo an early percutaneous transluminal coronary angioplasty, are recommended for eptifibatide therapy.<sup>66</sup> Eptifibatide may be administered with heparin and aspirin since it was used as a concomitant therapy in all the trials.

In adult patients with NSTEMI ACS and normal renal function, eptifibatide should be initiated as soon as possible as an intravenous bolus of 180 mcg/kg, followed by a continuous infusion (up to 72 hours) of 2.0 mcg/kg/min until hospital discharge or the initiation of coronary artery bypass graft surgery, up to 72 hours. In those undergoing PCI, the eptifibatide infusion should continue until hospital discharge or for up to 18–24 hours after the procedure (whichever comes first) to a maximum of 96 hours. In patients who are to undergo PCI, eptifibatide should be administered as an intravenous bolus dose of 180 mcg/kg immediately before the initiation of PCI, followed by a continuous infusion of 2.0 mcg/kg/min and a second bolus dose of 180 mcg/kg 10 min after the first bolus dose. The eptifibatide infusion should continue until hospital discharge or for up to 18–24 hours; a minimum of 12 hours of infusion is recommended.

In patients with renal dysfunction [estimated creatinine clearance  $<3$  L/h ( $<50$  mL/min)] with non-ST segment

elevation ACS and/ or undergoing PCI, the dosage of the continuous infusion of eptifibatide should be modified to 1 mcg/kg/min.

Eptifibatide is contraindicated in patients with a history of bleeding diathesis, severe hypertension, major surgery within preceding 6 weeks, history of stroke within 30 days or any history of hemorrhagic stroke, dependency on renal dialysis, or known hypersensitivity to any component of the product.

Eptifibatide injection is supplied as a sterile solution in 10 mL vials containing 20 mg of eptifibatide and 100 mL vials containing either 75 mg of eptifibatide or 200 mg of eptifibatide. Vials should be stored refrigerated at 2–8 °C (36–46 °F).<sup>67</sup>

## Place in therapy

The most significant development in antiplatelet therapy in recent years has been the development of the intravenous GP IIb/IIIa receptor antagonists (eptifibatide, abciximab, tirofiban). These agents act at the final common pathway of thrombus formation to prevent the activation of platelets and coronary thrombosis. These GP IIb/IIIa agents differ in their pharmacologic properties that influence the time course and magnitude of platelet inhibition. Abciximab was the first of these agents to be developed. Abciximab has limited specificity, antigenicity, and a long biological half-life. Eptifibatide and tirofiban have greater selectivity, shorter half-lives, and limited antigenicity.

GP IIb/IIIa receptor antagonists have been evaluated as an adjunctive therapy in patients with ACS. The magnitude of the benefit in patients with ACS depends on patient-risk stratification, the timing of invasive strategies (including PCI), the concurrent use of antithrombotics, dose and choice of the GP IIb/IIIa receptor antagonist.<sup>68</sup> GP IIb/IIIa receptor antagonists are recommended in current treatment guidelines of the ACC/AHA.<sup>11</sup> In a meta-analysis of 31,402 patients with ACS who were not scheduled to undergo revascularization,<sup>31</sup> GP IIb/IIIa receptor antagonist treatment was associated with a 9% relative risk reduction in the incidence of death or MI at 30 days ( $P = 0.02$ ). This benefit was limited to patients with positive troponin levels or who were in need of early revascularization. Thus eptifibatide and tirofiban are recommended in conservatively managed patients only if there is continuing ischemia, positive cardiac biomarker levels or other high-risk factors. None of the GP IIb/IIIa antagonists are recommended in the routine management of low-risk, troponin-negative patients in whom early angiography is not intended.<sup>11,12</sup>



The clinical efficacy of eptifibatide in patients with NSTEMI/ACS and/or those undergoing PCI has been determined in several large randomized controlled trials (including IMPACT-II, ESPRIT, and PURSUIT). In the IMPACT-II trial<sup>46</sup> the risk reduction provided by eptifibatide (135 mcg/kg bolus dose then infusion with 0.5 or 0.75 mcg/kg/min) was statistically significant only in the treatment-received analysis of the lower dosage. The cause of this unexpected outcome was not initially recognized, but subsequent pharmacodynamic studies indicated that the inhibition of platelet aggregation in this study may have been overestimated and that a higher eptifibatide dosage was required. Using a double-bolus dose of 180 mcg/kg, 10 min apart, with concomitant drug infusion of 2.0 mcg/kg/min in patients with low-to-moderate risk coronary artery disease undergoing elective and urgent PCI with intracoronary stent placement, eptifibatide achieved significant reductions in death and ischemic complications.<sup>44</sup> The ESPRIT researchers concluded that the eptifibatide regimen used in this study was better than a strategy of reserving treatment for the bailout situation. The dosage regimen used in this trial is now the approved dosage regimen for eptifibatide initiated at the time of PCI in the US. Retrospective subgroup analyses of patients from the PURSUIT trial indicated eptifibatide was effective in those who underwent early PCI during the first 72 hours and that the most favourable 30-day outcomes (death or MI) occurred when PCI was conducted within 24 hours.

The combination of GP IIb/IIIa inhibitors with other antiplatelet agents, such as aspirin or clopidogrel, has been investigated in low- or intermediate-risk patients with coronary artery disease.<sup>69,70</sup> The ISAR-REACT<sup>70</sup> and the ISAR-SWEET (diabetic patients)<sup>69</sup> trials evaluated the benefits of abciximab in low-risk patients with coronary artery disease undergoing PCI and pretreated with a high loading dose of clopidogrel. Overall, there was no added benefit from abciximab treatment in these studies. In contrast, limited data support regimens that combine eptifibatide with other antiplatelet agents such as aspirin and clopidogrel (ie, a triple antiplatelet regimen). The role of adjunctive GP IIb/IIIa antagonists in patients treated with clopidogrel and aspirin requires further investigation, especially in regard to patients with different risk profiles (eg, high-risk patients who may require more potent antiplatelet regimens) and in regard to the timing of the dose of the thienopyridine.<sup>71</sup>

The INTERACT study demonstrated that enoxaparin can be substituted for unfractionated heparin in an

eptifibatide-containing regimen in high-risk patients with ACS, including those undergoing PCI. Data investigating the efficacy of bivalirudin in patients undergoing PCI treated with eptifibatide are limited. The CACHET and REPLACE-I and -II trials indicated the efficacy and tolerability of bivalirudin in combination with the planned/provisional use of GP IIb/IIIa receptor antagonists (including eptifibatide) in patients undergoing PCI.<sup>72-74</sup> Large comparative clinical trials are still required to definitively determine whether bivalirudin is an acceptable substitute for unfractionated heparin in combination with the planned use of eptifibatide in patients (especially those at high risk) undergoing PCI.

Pharmacoeconomic analyses using data from both the ESPRIT (patients undergoing PCI) and PURSUIT (patients with non-ST segment elevation ACS) trials have demonstrated favorable cost-effectiveness ratios for eptifibatide in these indications in various countries. Moreover, the PRICE study in patients undergoing PCI demonstrated that median total in-hospital costs were significantly lower in eptifibatide than abciximab recipients, with the difference in costs being attributed to higher acquisition costs within the abciximab-treated group.

Increased bleeding is a major concern for any agent that affects hemostasis. In the large placebo-controlled trials in patients with non-ST segment elevation ACS, including those undergoing PCI, the beneficial clinical effects of eptifibatide were predictably accompanied by an increase in bleeding complications, with most major bleeding episodes occurring at the site of vascular access. Major intracranial bleeds, stroke, or profound thrombocytopenia rarely occurred during eptifibatide treatment. A retrospective review of high-risk ACS patients treated with eptifibatide, abciximab, or tirofiban found that the incidence of bleeding complications did not differ significantly among the three agents.<sup>75</sup>

The efficacy of eptifibatide has been less well investigated in patients with STEMI than in those with non-ST segment elevation ACS. Preliminary data from the RAPIER study<sup>50</sup> suggests a role for the emergency administration of eptifibatide in patients with STEMI before primary angioplasty. Currently, several ongoing trials are investigating the role of eptifibatide in this setting.

The combination of eptifibatide with a fibrinolytic has demonstrated improvements in surrogate markers of reperfusion in patients with STEMI in phase II trials.

Given that the combination of abciximab plus reduced-dose fibrinolytic was associated with a significantly higher incidence of major and minor bleeding than treatment with a fibrinolytic [GUSTO-V<sup>76</sup> and ASSENT-3,<sup>77</sup> studies that are

sufficiently powered for tolerability endpoints are required before firm conclusions can be drawn regarding the effect of a combination of eptifibatide and reduced-dose fibrinolytic on the incidence of major hemorrhage. Large randomized trials are also needed to establish the tolerability of various combinations and dosages of GP IIb/IIIa receptor antagonists, fibrinolytics, and antithrombotic agents, with careful attention being given to those patients at high risk of bleeding.<sup>78</sup>

To conclude, several large clinical trials provide evidence that intravenous eptifibatide is effective as adjunctive therapy to standard therapy in patients with non-ST segment elevation ACS, especially in those undergoing PCI. The ESPRIT trial demonstrated that in patients undergoing PCI with stenting, eptifibatide achieved significant reductions in death and ischemic complications compared with placebo. Similarly, the PURSUIT trial showed that in patients with non-ST segment elevation ACS, eptifibatide was associated with a significant reduction in the incidence of death or MI compared with placebo. Eptifibatide is well tolerated in these indications. Several ongoing trials are currently investigating the efficacy and tolerability of eptifibatide along with other agents in STEMI and other indications.

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