

# CASE REPORT

## Prolonged Infusion of Eptifibatide as Bridge Therapy Between Bare-Metal Stent Insertion and Cardiovascular Surgery: Case Report and Review of the Literature

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Dual antiplatelet therapy with aspirin and clopidogrel is the standard of care after coronary artery stent insertion. Clopidogrel, however, has been associated with an increased risk of bleeding if it is used before coronary artery bypass grafting (CABG), and current guidelines recommend that it be discontinued at least 5 days before surgery. Compared with dual antiplatelet therapy, single antiplatelet therapy or the combination of an antiplatelet agent and an anticoagulant is associated with an increased risk of subacute stent thrombosis. Management of patients who require semiurgent CABG after stent insertion presents a clinical challenge. Intravenous glycoprotein IIb/IIIa inhibitors provide antiplatelet coverage with a shorter duration of action; thus, in theory, they may be useful for these clinical situations. We describe a 47-year-old man who came to the emergency department with sudden-onset, retrosternal chest pain. An electrocardiogram confirmed a diagnosis of ST-segment elevation myocardial infarction. The patient underwent angioplasty and received a bare-metal stent. Because significant disease was revealed in other arteries, CABG was scheduled. Clopidogrel was discontinued in preparation for surgery, and the patient received an infusion of eptifibatide 2 µg/kg/minute as bridging therapy to surgery for a total of 9 days. No major hemorrhagic or clinically evident thrombotic complications occurred before or after the surgery. Eptifibatide may be safe and effective as bridging therapy for patients with intracoronary stents who require CABG.

**Key Words:** stent, eptifibatide, hemorrhage, coronary artery bypass grafting. (Pharmacotherapy 2010;30(4):127e–133e)

Antiplatelet therapy is an important component of management of ST-segment elevation myocardial infarction and is used to minimize the risk of stent thrombosis in patients undergoing percutaneous coronary intervention

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(PCI). For patients who undergo bare-metal stent insertion, current recommendations of the American College of Cardiology (ACC) are to continue clopidogrel in combination with aspirin for at least 1 month, and ideally up to 12 months, to minimize the risk of stent thrombosis.<sup>1</sup> This is a class I, level B recommendation, meaning that the procedure or treatment is useful and/or effective, with limited evidence from a single randomized trial or nonrandomized studies. For patients who have an increased risk of bleeding, the drug combination should be given for a minimum of 2 weeks.<sup>1</sup>

Stent thrombosis occurs most commonly in the first month after stent placement, and it carries a

significant risk of morbidity and mortality.<sup>1</sup> For patients who receive only aspirin therapy after insertion of a bare-metal stent, the risk of experiencing a major adverse cardiovascular event, defined as cardiac death, acute myocardial infarction, or repeat target vessel revascularization within 30 days, is 3.6–3.9%, compared with 0.5–0.8% when the patients receive dual antiplatelet therapy.<sup>2,3</sup>

For patients receiving clopidogrel in whom coronary artery bypass grafting (CABG) is planned, the ACC recommends stopping the clopidogrel for a minimum of 5 days, and preferably 7 days, before the surgery (class I, level B recommendation).<sup>4</sup> This recommendation depends on the urgency of revascularization and the risks of bleeding. The current guidelines do not address the issue of managing antithrombotic therapy specifically in patients undergoing CABG within 4 weeks of bare-metal stent insertion.

In contrast, current guidelines from the American College of Chest Physicians recommend continuing aspirin and clopidogrel in the perioperative period for patients requiring surgery within 6 weeks of placement of a bare-metal stent (grade 1C recommendation: strong recommendation but low- or very low-quality evidence).<sup>5</sup> These same guidelines suggest that clopidogrel be resumed—in all patients, not just those who received a coronary stent—24 hours after surgery if adequate hemostasis is confirmed (2C recommendation: weak recommendation with low- or very low-quality evidence). The guidelines recommend against routine bridging therapy with unfractionated heparin, low-molecular-weight heparin, direct thrombin inhibitors, or glycoprotein IIb-IIIa inhibitors (grade 1C recommendation). However, the American College of Chest Physicians recognizes that the use of short-acting antiplatelet agents holds promise in the perioperative setting due to the rapid reversal of their antiplatelet effects.

Patients who require semiurgent surgery soon after coronary artery stent placement present a clinical challenge. Discontinuation of clopidogrel too soon after stent insertion puts patients at risk for subacute stent thrombosis. However, use of clopidogrel within 5 days of surgery increases patients' risk of bleeding. Bridging with a short-acting intravenous antiplatelet agent may be the solution.

We describe a patient who received bridging therapy with the glycoprotein IIb-IIIa inhibitor, eptifibatide, for 9 days after receiving a bare-

metal stent and before undergoing CABG.

### Case Report

A 47-year-old man with a history of type 2 diabetes mellitus, hypertension, and dyslipidemia presented to the emergency department after developing sudden-onset, retrosternal chest pain. An electrocardiogram showed ST-segment elevation in leads II, III, aVf, V4, V5, and V6, and ST-segment elevation myocardial infarction was diagnosed. While in the emergency department, the patient developed ventricular fibrillation requiring resuscitation. He was given clopidogrel 600 mg and aspirin 160 mg. Unfractionated heparin was started as a 5000-unit bolus followed by a continuous infusion of 1000 units/hour for 1 hour. The patient was taken to the cardiac catheterization laboratory where angiography revealed occlusion of the proximal right coronary artery, with severe stenosis of the left main, proximal left anterior descending, and left circumflex coronary arteries. At this time, the patient underwent successful PCI of the proximal right coronary artery with bare-metal stent insertion. During PCI, the patient received an additional 1700 units of heparin, as well as abciximab as a 0.25- $\mu$ g/kg bolus followed by a 0.125- $\mu$ g/kg/min infusion. After PCI, abciximab was continued for 12 hours. The heparin infusion was restarted 4 hours after sheath removal and discontinued 2 days after PCI. Antiplatelet therapy was restarted with aspirin 81 mg/day and clopidogrel 75 mg/day. The patient also restarted his home drug therapy, which consisted of metoprolol, ramipril, and atorvastatin.

On hospital day 2, given the patient's extensive coronary artery disease, it was decided that he would undergo CABG; he was to remain hospitalized while awaiting surgery due to the burden of left main coronary disease. Clopidogrel was discontinued, and subcutaneous enoxaparin 1 mg/kg twice/day was started. Because of a concern about subacute stent thrombosis with the discontinuation of clopidogrel, the decision was made to administer bridge therapy to surgery with the short-acting, reversible antiplatelet agent eptifibatide. This was done to ensure that the patient continued to receive dual antiplatelet therapy. Because the patient had normal renal function, an infusion of eptifibatide at 2  $\mu$ g/kg/minute was started on day 3. A bolus was not given because the patient had received clopidogrel as a loading dose and because he had received 2 days of clopidogrel

therapy. Therefore, immediate antiplatelet activity was not thought to be required.

The patient also continued to receive aspirin 81 mg/day. This dosage was used since the patient was receiving triple antithrombotic therapy (aspirin, eptifibatide, and enoxaparin); therefore, his risk for bleeding complications was judged to be high. In addition, current evidence for aspirin doses above 81 mg/day does not come from randomized controlled trials (ACC class I, level B recommendation).<sup>1</sup>

Although the patient was listed for semiurgent CABG, circumstances beyond control delayed surgery for 12 days after PCI. External factors determined the final duration of therapy with eptifibatide and enoxaparin rather than a predetermined need to treat the patient for this length of time before surgery. The patient received eptifibatide therapy for a total of 9 days. He did not report any chest pain during the period between PCI and CABG, and no as-needed sublingual nitroglycerin was used. Electrocardiograms were monitored daily, and no ST-segment changes were noted.

Enoxaparin and eptifibatide were discontinued 24 and 8 hours, respectively, before surgery; aspirin was withheld the morning of surgery. During the surgery, three mediastinal chest tubes were inserted and remained in place for 48 hours afterward. Total drainage of serosanguineous fluid was 150 ml; this volume favorably compares with the 24-hour drainage of 597–1105 ml reported from an observational study using eptifibatide before CABG.<sup>6</sup>

The four-vessel CABG was successful, and the patient resumed therapy with aspirin 81 mg/day 6 hours after the surgery. Clopidogrel was restarted on postoperative day 5. No major or minor hemorrhagic complications occurred during the patient's hospitalization, nor did he require any blood transfusions. The patient's hemoglobin concentration before surgery was 13.6 g/dl (normal range 13.5–17.5 g/dl) and dropped to 10.0 g/dl after surgery. At discharge, 5 days after CABG, his hemoglobin level was 9.6 g/dl. These postoperative changes were within the acceptable limits designated at our institution. His platelet count remained stable throughout his admission in the range of 322–377  $\times 10^3/\text{mm}^3$  (normal range 140–450  $\times 10^3/\text{mm}^3$ ).

## Discussion

Clopidogrel is a thienopyridine derivative. Its active metabolite inhibits platelet aggregation by

preventing the binding of adenosine 5'-diphosphate to its platelet receptor subtype P2Y<sub>12</sub>. This then inhibits the activation of the glycoprotein IIb-IIIa receptor complex.<sup>7</sup> Within 2 hours of a loading dose of clopidogrel 300–600 mg, 40–60% of adenosine 5'-diphosphate-induced platelet aggregation is blocked, and this level of inhibition is maintained at doses of 75 mg/day.<sup>8</sup> Clopidogrel-induced platelet inhibition is irreversible, and the antiplatelet effect can persist for 7–10 days after therapy is discontinued.<sup>7, 8</sup> Current recommendations concerning clopidogrel and CABG indicate that clopidogrel should be stopped for at least 5 days, and preferably 7 days, before surgery.<sup>4</sup>

To our knowledge, no randomized controlled trials have directly examined the bleeding risk clopidogrel confers in patients undergoing CABG. Available data are from post hoc analyses in patients with acute coronary syndromes (ACS) who required CABG, as determined by their physicians, in trials comparing clopidogrel with placebo. A meta-analysis and a structured review have explored this issue.<sup>9, 10</sup> The meta-analysis included 4002 patients, 605 of whom underwent cardiac surgery while receiving clopidogrel.<sup>9</sup> This analysis demonstrated a significant increase in blood loss (weighted mean difference 323.62 ml, 95% confidence interval [CI] 137.19–510.04) and in the requirement for transfusion of any blood product (odds ratio 4.90, 95% CI 2.79–8.59) among patients receiving clopidogrel versus those who had not. The structured review included data on 13,475 patients, 3505 of whom received clopidogrel within 7 days before CABG.<sup>10</sup> Clopidogrel-exposed patients had significantly higher chest tube output in four of seven comparisons and significantly greater platelet transfusion requirements in 10 of 11 studies. Also reported was a trend toward increased repeat operation rates for uncontrolled bleeding and cardiac tamponade.

The largest single data set is from the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial, a randomized controlled study of 12,562 patients with ACS but without ST-segment elevation.<sup>11</sup> The findings demonstrated the superiority of the combination of aspirin and clopidogrel compared with aspirin alone with respect to the composite end point of death from cardiovascular causes, nonfatal myocardial infarction, or stroke.

A total of 2072 patients from this trial underwent CABG during initial hospitalization

**Table 1. Bleeding Outcomes in Patients Who Received a Glycoprotein IIb-IIIa Inhibitor Before CABG<sup>6, 21-25</sup>**

Study Design	Proportion of Patients from		Mean Chest Tube Output (ml/24 hrs)	Percentage of Patients		
	Original Trial	Intervention		Major Bleed	Transfusion	Death
Retrospective review of EPIC trial data (n=58) <sup>21</sup>	2.8%	Placebo (n=25)	NR	72	64	8
		Abciximab 0.25-mg/kg bolus + 10-µg/min infusion (n=17 <sup>a</sup> )	NR	77	77	29
Consecutive medical record review of patients requiring emergency CABG who received abciximab (n=11) <sup>22</sup>	NA	Abciximab 0.25-mg/kg bolus + 10-µg/min infusion stopped ≤ 12 hrs before CABG (n=6)	1543	NR	83	16
		Abciximab 0.25-mg/kg bolus + 10-µg/min infusion stopped > 12 hrs before CABG (n=5)	395	NR	40	0
Retrospective medical record review of patients who received tirofiban or heparin before CABG (n=88) <sup>23</sup>	NA	Tirofiban 0.4-µg/kg/min bolus + 0.1-µg/kg/min infusion (n=20)	354.5	NR	10	NR
		Heparin (n=68)	544.4	NR	41	NR
Retrospective review of PURSUIT trial data (n=1558) <sup>24</sup>	14%	Eptifibatide 180-µg/kg/min bolus + 2-µg/kg/min infusion (n=866)	NR	58.2	NR	19.7
		Placebo (n=692)	NR	56.6	NR	25.1
Retrospective review of PURSUIT trial data (within 2 hrs of drug discontinuation) (n=78) <sup>25</sup>	0.7%	Eptifibatide 180-µg/kg/min bolus + 2-µg/kg/min infusion (n=32)	NR	60	59	6.3
		Placebo (n=46)	NR	60	57	6.5
Open-label, observational study of patients undergoing CABG 2 or 4 hrs after eptifibatide administration (n=14) <sup>6</sup>	NA	Eptifibatide 2 µg/kg/min stopped 2 hrs before CABG (n=9)	1105	NR	67	0
		Eptifibatide 2 µg/kg/min stopped 4 hrs before CABG (n=5)	597	NR	20	20

CABG = coronary artery bypass grafting; EPIC = Evaluation of c7E3 Fab in the Prevention of Ischemic Complications; NA = not applicable; NR = not reported; PURSUIT = Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy.

<sup>a</sup>Sixteen patients received only the bolus dose of abciximab; as this regimen is not standard clinical practice, their data were not included in the results.

or follow-up.<sup>12</sup> Major bleeding was reported in 7.5% of patients given placebo compared with 9.6% of patients receiving clopidogrel (risk ratio 1.27, 95% CI 0.96–1.69). Bleeding rates were analyzed according to discontinuation of the study drug at 5 or fewer days before surgery versus more than 5 days. This analysis revealed no excess in any bleeding for patients in whom the drug was stopped more than 5 days before surgery. For those continuing the drug within 5 days of surgery, a nonsignificant excess in major bleeding was observed.

Given the concerns regarding bleeding among patients receiving clopidogrel immediately before CABG, it is important to consider other options for preventing stent thrombosis. Several randomized controlled trials have been conducted to compare the antiplatelet strategy of aspirin and ticlopidine with oral anticoagulation after stent insertion.<sup>13-16</sup> Antiplatelet therapy demonstrated benefit over anticoagulation for the prevention of cardiac events, with a decrease in bleeding

complications.<sup>13, 14, 16</sup> Data from these trials support the concept that bridging to CABG with anticoagulation alone after stent insertion is less effective than other approaches and that it increases the risk of hemorrhagic complications.

Short-acting antiplatelet agents, such as the intravenous glycoprotein IIb-IIIa inhibitors, are another option for bridging between stent insertion and CABG. The binding of ligands to the glycoprotein IIb-IIIa receptor is the final common pathway of platelet aggregation. Antagonists of this platelet receptor produce greater than 80% inhibition of platelet aggregation, far exceeding that achieved by aspirin or clopidogrel.<sup>17</sup> Several intravenous agents, including abciximab, tirofiban and eptifibatide, are available; however, we know of no randomized studies of the bleeding risks these agents potentially confer in patients who require CABG. Data from a post hoc and subgroup analysis provide some insight into the safety of these agents when they are used before CABG.

### Abciximab

Abciximab is a monoclonal antibody that binds to platelet IIb-IIIa receptors and inhibits platelet aggregation. Onset of antiplatelet action is rapid; however, reversibility of this effect is delayed. Bleeding times may normalize within 12 hours after abciximab is discontinued. However, platelet activity may take up to 48 hours to return to baseline, and low levels of abciximab may be detected 14 days after discontinuation of therapy.<sup>17-19</sup>

The Evaluation of c7E3 Fab in the Prevention of Ischemic Complications (EPIC) trial demonstrated the benefit of abciximab versus placebo in 2099 patients undergoing high-risk PCI.<sup>20</sup> Fifty-eight patients required CABG. Major blood loss and mortality rates nonsignificantly increased in the groups who received abciximab versus placebo (Table 1).<sup>21</sup>

A medical record review of 11 patients who received abciximab during PCI and who required emergency cardiac surgery found more bleeding complications if abciximab was given within 12 hours of surgery compared with those in whom the drug was stopped more than 12 hours before surgery (Table 1).<sup>22</sup>

The prolonged antiplatelet effects of abciximab make it a less-than-ideal choice for bridging therapy.

### Tirofiban

Tirofiban is another rapid-acting glycoprotein IIb-IIIa inhibitor. However, reversibility of its antiplatelet effect is much quicker than that of abciximab, with a return of baseline bleeding times within 4–8 hours after discontinuation of the drug.<sup>18</sup>

Investigators from the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-Plus) study found clinical benefit with the combination of tirofiban and heparin versus heparin alone in 1915 patients with ACS.<sup>26</sup> Nine patients in the tirofiban-heparin group and 16 in the heparin-only group underwent urgent CABG.<sup>27</sup> Severe or life-threatening bleeding occurred in two (22%) of nine patients in the tirofiban group compared with one patient (6%) in the heparin group. Clinical events and bleeding episodes before and after CABG were not reported separately.

Investigators retrospectively assessed bleeding complications in 88 patients who underwent urgent or emergency CABG after being diagnosed

with ACS.<sup>23</sup> Hemoglobin values were higher in the group given tirofiban than those receiving heparin; the tirofiban group required fewer transfusions and had less chest-tube drainage (Table 1). Other investigators retrospectively assessed the risk of hemorrhage in 40 patients by timing of tirofiban discontinuation: more than 8 hours versus 8 hours or less before surgery.<sup>28</sup> They found no significant differences in post-operative coagulation parameters, nor did they identify a relationship between the timing of tirofiban discontinuation and blood loss during the first 24 hours after surgery.

Given the limited and conflicting data regarding the use of tirofiban before cardiovascular surgery, it is not an ideal choice for bridging therapy.

### Eptifibatide

Eptifibatide is a highly specific, reversible antagonist of the glycoprotein IIb-IIIa receptor. Compared with abciximab and tirofiban, eptifibatide provides the most consistent level of platelet inhibition throughout the infusion.<sup>29</sup> When eptifibatide is given at the recommended dosage of an 180- $\mu$ g/kg bolus followed by a 2- $\mu$ g/kg/minute infusion, greater than 80% platelet inhibition is achieved within 1 hour.<sup>30</sup> Giving eptifibatide as a 90- $\mu$ g/kg bolus followed by a 1- $\mu$ g/kg/minute infusion produces 64% platelet inhibition within 1 hour.<sup>30</sup> This lower dosage produces a platelet inhibition rate similar to clopidogrel. Recovery of platelet aggregation is apparent within 4 hours after the infusion is completed.<sup>19</sup>

The Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis (IMPACT)-II study was a randomized controlled trial of two dosing regimens of eptifibatide compared with placebo in 4010 patients scheduled for elective, urgent, or emergent coronary intervention.<sup>31</sup> The results demonstrated no significant difference in rates of major bleeding during CABG. The Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial demonstrated that a bolus and high-dose infusion of eptifibatide reduced the composite end point of death or myocardial infarction in 10,948 patients requiring nonurgent coronary stent placement.<sup>32</sup>

Researchers then conducted a post hoc analysis of the 1558 patients from the PURSUIT trial who underwent in-hospital CABG.<sup>24</sup> The median

duration of treatment was 71.9 hours for patients receiving placebo compared with 71.8 hours for those receiving eptifibatide. The median time between discontinuation of treatment and CABG was 57.8 hours in the placebo group and 66.5 hours in the eptifibatide group. No significant differences in bleeding end points were found between the groups (Table 1).

Another post hoc analysis of data from the PURSUIT study addressed clinical end points in 78 patients who underwent CABG within 2 hours of randomization.<sup>25</sup> Thirty-two patients who received eptifibatide before surgery had clinical outcomes similar to the 46 patients who received placebo (Table 1).

Results from the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrelin Therapy Trial (ESPRIT) supported the use of a double bolus of eptifibatide compared with placebo in 2064 patients scheduled to undergo nonurgent coronary stent insertion.<sup>33</sup> Eleven patients in ESPRIT underwent urgent CABG, and reported bleeding rates within 48 hours of CABG were similar for the placebo and eptifibatide groups.<sup>27</sup>

Use of eptifibatide preoperatively does not appear to increase bleeding rates. Further information regarding this issue is available from an open-label observational study on the pharmacokinetics of eptifibatide during CABG with cardiopulmonary bypass.<sup>6</sup> Fourteen patients completed the trial (Table 1). The authors concluded that patients could safely undergo CABG within 4 hours after discontinuing eptifibatide.

Data regarding the efficacy of glycoprotein IIb-IIIa inhibitors as antiplatelet agents for patients with an intracoronary stent are limited. After an extensive literature search, we identified only a single case report in which eptifibatide was used as the antiplatelet agent in a patient who had received a bare-metal stent; however, this case did not involve CABG.<sup>34</sup> The patient experienced massive hemorrhage at the gastroesophageal junction and required truncal vagotomy and gastroenterostomy 6 days after insertion of the bare-metal stent. The patient received eptifibatide because of an inability to receive oral antiplatelet therapy. Eptifibatide was infused for 8 days, during which the patient was hemodynamically stable with no evidence of myocardial ischemia or bleeding. A recurrent upper gastrointestinal hemorrhage necessitated the discontinuation of eptifibatide. Four hours later, the patient had another myocardial infarction, which was attributed to recurrent stent thrombosis.

## Conclusion

Our experience is consistent with that reported in the literature in that no major hemorrhagic complications occurred in our patient receiving eptifibatide, even with treatment for 9 days. In addition, our patient did not demonstrate any clinical or diagnostic evidence that suggested compromised stent patency despite his not receiving clopidogrel for 14 days.

The available literature on the use of glycoprotein IIb-IIIa inhibitors before CABG is lacking, which limits its applicability to our case. Most of the literature involves populations without ST-segment elevation myocardial infarction. In addition, none of the trials were randomized or specifically designed to evaluate the safety of using these agents before CABG. Furthermore, we identified no head-to-head comparisons of the various glycoprotein IIb-IIIa inhibitors with respect to their safety before CABG. Therefore, one cannot assume that one agent is better than the others. Efficacy data regarding these agents in patients who have received an intracoronary stent are limited to a single case report. Thus, additional research is needed to evaluate the efficacy and safety of using a glycoprotein IIb-IIIa inhibitor before CABG and of using it as a potential bridging agent for patients who have received an intracoronary stent.

This case report and review of the literature support the effectiveness and safety of eptifibatide as bridge therapy to CABG after coronary stenting with a bare-metal stent. For patients who urgently require major surgery after intracoronary stent insertion and in whom clopidogrel is to be avoided, discontinuing clopidogrel 5–7 days before surgery and starting eptifibatide for up to 9 days may be a reasonable option to minimize the risk of stent thrombosis. Clopidogrel therapy should be resumed as soon as possible after the procedure once hemostasis is achieved. Clinicians could consider reducing the dose of eptifibatide to produce platelet inhibition consistent with that achieved with dual antiplatelet therapy. Clinicians should balance the cost and safety implications of this treatment strategy against the risk and consequences of possible stent thrombosis.

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