

**Treatment Strategies for the Prevention of Ischemic Complications in
Patients Undergoing Percutaneous Coronary Intervention
with Stent Placement**

Pharmaceutical Care Project
Outcomes Literature Evaluation
Final Draft

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Introduction

Coronary stenting has evolved into the most frequent revascularization procedure performed in cardiac catheterization labs across the world, and is used in over 80% of all procedures.¹ The primary complication associated with stent placement is thrombosis in the target vessel, which can result in death, myocardial infarction (MI), or the need for emergency revascularization by means of coronary artery bypass graft (CABG) or a repeat percutaneous coronary intervention (PCI). Variables associated with increased mortality in patients undergoing PCI include advanced age, female gender, diabetes, prior MI, multi-vessel disease, a large area of myocardium at risk, pre-existing impairment of left ventricular (LV) function, impaired renal function, and collateral vessels supplying significant areas of myocardium that originate distal to the segment to be dilated.²⁻³ Stents have been shown to reduce both the risk of major complications and late-term restenosis.⁴

Several antiplatelet strategies have been studied in the prevention of ischemic complications in patients undergoing PCI with stent placement. Glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, including abciximab, eptifibatid, and tirofiban, inhibit the final common pathway for platelet aggregation, and have been widely studied in this setting. Each agent differs in regard to duration of action at the platelet target receptor, receptor affinity, and binding sites on the GP IIb/IIIa receptor. Abciximab binds to at least two other integrins expressed in endothelial cells and monocytes. They also differ in regard to cost.⁵ The first of the GP IIb/IIIa inhibitors, abciximab was studied in the EPIC trial, and found significantly improved outcomes with regard to the composite endpoint of death, MI, and urgent target vessel revascularization (UTVR), including long term survival benefits.⁶ That study also found a significantly higher incidence of bleeding complications which led to the now reduced dose of heparin used with GP IIb/IIIa inhibitors.⁷ Two other trials, IMPACT II (eptifibatid) and RESTORE (tirofiban), did not find statistically significant differences in the composite endpoint in patients undergoing balloon angioplasty or atherectomy, though there were trends toward a decrease in events.⁸⁻⁹

Since these earlier trials were conducted, thienopyridines have been added to the arsenal of antiplatelet therapy. Thienopyridines such as clopidogrel and ticlopidine have been shown to have a synergistic anti-platelet effect when given with aspirin, and the combination has been shown to be superior to aspirin alone or aspirin plus oral anticoagulation in patients receiving stents.¹⁰⁻¹¹

Lastly, a direct thrombin inhibitor, bivalirudin, has been studied as an option that may be as effective as heparin plus GP IIb/IIIa inhibitors with less incidence of major and minor bleeding as well as decreased cost.

Each of these strategies is not without adverse effects, the foremost of which is major and minor bleeding complications. Several questions remain to be answered. Is one agent more effective than another? Is there a survival benefit related to the use of these agents with stenting procedures? Are there other agents available that would be equally as effective? The purpose of this paper is to review five published trials involving strategies of antiplatelet therapy to prevent ischemic complications in patients undergoing PCI.

Evaluation of Studies

ESPRIT, EPISTENT, and TARGET

Since the EPIC trial, abciximab has been the preferred agent for many interventional cardiologists because it was the only agent to show survival benefit in the earlier trials. With the onset of stenting, several new trials were published including ESPRIT (eptifibatide), EPISTENT (abciximab) and TARGET (tirofiban and abciximab).¹²⁻¹⁴ There are many similarities between these three trials. Each included the composite primary endpoint of Death, MI, and UTVR at 30 days. In addition, ESPRIT also included GP IIb/IIIa bailout within 48hrs of procedure. All patients received aspirin as well as thienopyridine prior to the procedure. ESPRIT and EPISTENT were randomized, double-blind, placebo controlled trials of similar size. Each trial showed a significant decrease in the occurrence of the composite primary outcome measures as compared to placebo, with a rate of 5.3% in the stent/abciximab group ($p < 0.001$) and 6.6% in the eptifibatide group ($p = 0.0015$).

There are also several distinct differences in the two trials. ESPRIT enrolled patients who were to undergo elective PCI, and in the opinion of the treating physician, would not routinely be treated with glycoprotein IIb/IIIa inhibitors. It was therefore a low risk patient population as compared to EPISTENT, which included a higher risk group of patients undergoing both elective and urgent PCI. ESPRIT utilized high inflation deployment stents, the standard of practice based on clinical trials to date, whereas EPISTENT utilized an older low-inflation deployment stent.⁴ Although the event rate for abciximab/stent appears lower than that of eptifibatide, there are several reasons why primary outcome measures may have been under-reported in the EPISTENT trial. First, creatinine kinase MB isoenzymes (CK-MB) were not routinely monitored for the first 24hrs after PCI, therefore events may have been missed, particularly non-Q MI's. Second, the investigators defined MI as CK-MB of 5X the upper limit of normal (ULN). ACC/AHA guidelines recommend 3X the ULN for identifying an MI after PCI.⁴ Lastly, 30.3% of patients in the placebo group had >1 stent placed vs 26% in the abciximab group. The ESPRIT trial may

also have missed primary outcome measures. While their criteria for MI included CK-MB 3X ULN as their threshold for MI, they also chose not to routinely monitor CK-MB. Also the use of GP IIb/IIIa bailout may have decreased the event rate in the placebo arm. Interestingly, the greatest decrease in the primary event rate in the EPISTENT trial occurred in men (10.5% placebo vs 4.2% stent plus abciximab (SA) $p < 0.001$), diabetics (12.1% placebo vs 5.6% SA $p = 0.04$) and patients < 65 years of age (10.2% placebo vs 3.6% SA).

TARGET is the only head-to-head trial of two GP IIb/IIIa inhibitors, abciximab and tirofiban, which enrolled more than twice the number of patients as the previous two trials.¹⁴ The study utilized the higher dose of tirofiban from the RESTORE trial rather than the current Food and Drug Administration (FDA) approved dose, and enrolled a higher risk patient population, those undergoing both elective and urgent PCI, similar to EPISTENT. Of the trials evaluated, TARGET is the only trial to measure CK-MB routinely during the first 24hrs following PCI utilizing 3X the ULN as the threshold for MI. This may have accounted for a slightly higher event rate for abciximab, 6%, vs. that of 5.3% found in the EPISTENT trial. The investigators attempted to prove the non-inferiority of tirofiban to abciximab, however the difference in the occurrence of the primary composite endpoint was statistically significant, 7.6% for tirofiban and 6% for abciximab ($p = 0.038$) showing abciximab to be superior. Most of the benefit was derived from a decrease in non-fatal MI (tirofiban 6.9% vs abciximab 5.4% $p = 0.04$). None of the GP IIb/IIIa trials showed a statistically significant difference in the incidence of death. All three trials demonstrated that a large portion of the benefit was derived from a decrease in the occurrence of MI.

REPLACE II

REPLACE II was a large randomized double blind double dummy (active control) trial which enrolled 6,010 patients and evaluated bivalirudin plus provisional GP IIb/IIIa inhibitor vs heparin plus GP IIb/IIIa inhibitor.¹⁵ The study purpose was to prove the non-inferiority of bivalirudin with provisional GP IIb/IIIa inhibitor compared to heparin plus GP IIb/IIIa inhibitors. Abciximab or eptifibatide were approved for GP IIb/IIIa inhibitor use in this trial. The primary outcome measure included death, MI, UTVR, and in-hospital major bleeding. There was no statistically significant difference in the occurrence of the primary endpoint (9.2% bivalirudin versus 10% heparin plus GP IIb/IIIa, $p = 0.32$). The percentage of patients receiving provisional GP IIb/IIIa inhibitor therapy was 7.2%. The investigators measured CK-MB levels every 8 hrs for 24 hrs after PCI. Subgroup analysis of the triple composite endpoint of death, MI, or UTVR, showed that heparin plus GP IIb/IIIa inhibitor therapy was superior in all groups except women and patients > 75 yrs of age. There was not a statistically significant difference in the rate of death or MI between the two groups. Although there was a trend toward a higher rate of MI in the bivalirudin group, it is unclear whether provisional GP IIb/IIIa or bivalirudin alone is primarily responsible for this trend. There was a significant decrease in in-hospital major bleeding rates for bivalirudin (2.4% for bivalirudin vs 4.1% in the heparin/GP IIb/IIIa group). This

represents the highest rate of major bleeding among the studies evaluated thus far. ESPRIT reported a major bleeding rate of 1%, EPISTENT 1.5%, and TARGET 0.9% for tirofiban and 0.7% for abciximab.

ISAR-REACT

This most recent study was designed to show the superiority of abciximab plus clopidogrel vs clopidogrel alone.¹⁶ It enrolled patients scheduled to undergo elective PCI in a native coronary artery, a relatively low risk patient population similar to ESPRIT. Although the authors concluded that there was no statistically significant difference in the occurrence of the primary composite endpoint of death (0.3% abciximab and 0.3% clopidogrel), MI (4% abciximab and 4% clopidogrel) or UTVR (1% abciximab and 1% clopidogrel), the primary endpoints were measured by patient interviews conducted at 30 days after randomization. This potentially introduced bias into the results based on patient perceptions of their symptoms and patient understanding of the questions posed, and may again have led to an under-reporting of events. As in TARGET and REPLACE II, CK-MB levels were drawn every 8 hrs for 24hrs following PCI. Furthermore the investigators excluded patients with “insulin dependent diabetes mellitus”, a large subset of patients with coronary artery disease that have been shown to benefit from GP IIb/IIIa inhibition. Another difference in this study is that patients enrolled in Europe who were in the placebo group received 140 units of heparin/kg with no activated clotting time (ACT) monitoring. This accounts for about 95% of all patients enrolled in the study. Placebo patients in the United States received 100 units heparin/kg and maintained an ACT of 250-300sec. It is unknown whether these differences affected the study results.

SUMMARY

There were problems in each of the studies related to reporting of outcome measurements. There were also differences in the types of stents used. Despite these issues, eptifibatide and abciximab have been shown to significantly reduce death, MI, and UTVR in patients undergoing PCI with stent placement. While earlier data for patients undergoing PCI with balloon angioplasty or atherectomy indicated abciximab to be a superior choice for GP IIb/IIIa inhibition, there is no evidence to date which would indicate abciximab to be superior to eptifibatide in the setting of stent placement, particularly with doses adequate to induce sufficient platelet inhibition, and the newer, less thrombogenic stents now being utilized. High-risk patients seem to derive the greatest benefit from either abciximab or eptifibatide. Subgroup analysis in the EPISTENT trial might indicate that abciximab is a more appropriate choice for patients with diabetes; however, the study was not powered to detect such a difference. Therefore it would be premature to assume superiority of abciximab over eptifibatide in this population. The TARGET trial failed to show equivalence

between abciximab and tirofiban; the trial showed the superiority of abciximab in the primary composite endpoint. However, there was not a statistically significant difference in the rates of death or UTVR. It remains to be seen whether the decreased rate of MI translates into a long-term survival benefit. Tirofiban, with its differing pharmacokinetic and dynamic properties, needs further evaluation to determine the optimal dose to achieve >80% inhibition of the GP IIb/IIIa receptor, at which time it may prove to be an appropriate choice.

REPLACE II concluded that bivalirudin was not inferior to heparin plus GP IIb/IIIa inhibitor in the prevention of death, MI, or UTVR, and that it produced a decrease in major in-hospital bleeding rates. One of the reasons for the hope that bivalirudin would be effective is its decreased cost vs. that of GP IIb/IIIa inhibitors since it was infused only for the duration of the procedure. As discussed previously, the use of provisional GP IIb/IIIa inhibition at a rate of 7.2% in the bivalirudin group may have decreased the occurrence of the primary outcome in that group and therefore we cannot conclude that the two are equivalent without further study. Once more, while the study did show a significant decrease in the rate of major bleeding events in the bivalirudin group, the question remains as to why the rate for heparin/GP IIb/IIIa inhibitor was so different from the previously conducted trials, especially since both trials utilized the Thrombolysis in Myocardial Infarction criteria for major and minor bleeding.¹⁷

While the ISAR-REACT investigators concluded that clopidogrel 600mg may be appropriate without the addition of GP IIb/IIIa inhibitor in certain low risk patients, the exclusion of "insulin dependent diabetes mellitus" patients and the method by which the investigators measured endpoints as well as the method and dose of heparin administration during the procedure would indicate that further study is needed.

RECOMMENDATIONS

Based on evaluation of these five trials, patients undergoing PCI with stent placement should receive aspirin, thienopyridine as well as GP IIb/IIIa inhibitor. Abciximab and eptifibatide are both appropriate therapy for high-risk patients, including those with multiple target lesions, diabetes and renal failure. There is much supposition about the possible additional benefits of abciximab, which binds to at least two other integrins expressed in endothelial cells and monocytes, which may further influence the adhesion of platelets and endothelial cells as well as platelets and white cells.⁵ These potential differences are yet to be elucidated. Eptifibatide also showed significantly lower rates of bleeding and thrombocytopenia as compared to abciximab. Eptifibatide is therefore a cost effective alternative (\$400-\$500/patient) compared to abciximab (\$1350.00/patient).

Long-term studies are still lacking for the use of bivalirudin in the PCI setting, therefore, it cannot yet be recommended as monotherapy for patients undergoing stent placement but is an alternative for patients who are unable to

receive heparin or are at a higher risk for bleeding complications. Bivalirudin may actually be added to GP IIb/IIIa inhibitor since 7.2% of patients in REPLACE II received both agents without a higher incidence of bleeding complications.

Although a high loading dose of clopidogrel yields additional platelet inhibition, it cannot be recommended as monotherapy in patients undergoing PCI with stent placement until long-term studies are conducted.

These recommendations are consistent with the recently published consensus guidelines.¹⁸ The guidelines are more specific with regard to medication choice in different types of MI. The five trials reviewed in this evaluation were not powered to detect differences to this detail.

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Table 1
Summary of evaluated clinical trials

Study	Trial Design	# of subjects	Inclusion criteria	Exclusion Criteria
EPISTENT	R DB PI Ct Multicenter trial in the U.S. and Canada. Duration: 30 days	2399	Elective or urgent revascularization (UR) with at least 76% stenosis in target lesion that is not an unprotected left main.	Bleeding diathesis, intracranial neoplasm, hx of stroke in the past 2 yrs, uncontrolled HTN (SBP >180 or DBP >100), recent surgery or PCI within the past 3 mos, concurrent warfarin therapy or an INR >1.5
ESPRIT	R DB PI Ct crossover permitted Multicenter trial in the U.S. and Canada Duration: 30days	2064	Patients scheduled to undergo PCI with stent implantation in a native coronary artery and who would not routinely be treated with GP IIb/IIIa inhibitors	MI in the last 24hrs, continuing CP, PCI in the last 3 mos, previous stent in target lesion, anticipated staged PCI in 30 days after randomization, GP IIb/IIIa inhibitor or thienopyridine 30 days before randomization, stroke or TIA in the last 30 days, any hx of hemorrhagic stroke, hx of bleeding diathesis or abnormal bleeding within the last 30 days, major surgery in the last 6 wks, uncontrolled HTN (SBP >200 or DBP >100), documented thrombocytopenia (<100,000) or Scr >350mc mol/L
TARGET	R DB active control (double dummy) Multicenter trial in 18 countries Duration: 30 days	4809	Patients to undergo coronary stenting procedure (elective or urgent) of a newly stenotic or restenotic atherosclerotic lesion in a native vessel or a bypass graft. All lesions that were judged to have stenosis of more than 70% on angiography had to be amenable to stenting.	Patients with cardiogenic shock, acute MI with ECG evidence of ST-segment elevation, SCr >2.5, ongoing bleeding or bleeding diathesis including a plt count of <120,000.
REPLACE II	R DB active control (double dummy) Multicenter trial in 9 countries Duration: 30days	6010	>21 years of age and scheduled to undergo PCI with an approved device.	PCI performed as reperfusion therapy for acute MI, poorly controlled HTN (SBP >180 or DBP >100), unprotected LM stenosis of >50%, pregnancy, PCI in the last 30 days or planned staged PCI within the next 30 days, active internal bleeding or bleeding diathesis, surgery, trauma or GI or genitourinary tract bleeding in the last 6wks, prior intracranial bleeding or structural abnormality. PLT <100,000, SCr >4 or dialysis, bivalirudin within the last 24hrs, warfarin therapy, unfractionated heparin in the last 6hrs, LMWH in the last 8hrs, abciximab in the last 7days, eptifibatide or tirofiban in the last 12 hrs.
ISAR-REACT	R DB PI Ct Multicenter trial in Europe and the U.S. (5% of patients enrolled) Duration: 30 days	2159	Patients to undergo elective PCI in a native coronary artery	MI in the last 14 days, US with ST changes in 2 leads at rest, Troponin T of >0.03ng/ml, target lesion in a graft, chronic occlusion present for >3 mos, target lesion with angiographically visible thrombus, EF <30%, hemodynamic instability, IDDM, pericarditis, cancer, stroke in prior 3mos, active bleeding or bleeding diathesis, trauma or major surgery in the last month, suspected aortic dissection, oral anticoagulation, GP IIb/IIIa inhibitor within the last 14 days, severe uncontrolled HTN (SBP>180), Hgb <10, HCT <34%, PLT <100,000 or >600,000, known allergic reaction to the study medication, pregnancy

Table 1 (cont)

Study	Treatment Regimens Evaluated	Outcome variables and methods of measurement	Major Findings
EPISTENT	<p>Stent + placebo + heparin (hep) 100 units/kg and maintain ACT 300sec</p> <p>Stent + abciximab(0.25mcg/kg bolus and 0.125mcg/kg/min infusion x 12hrs) + hep 70 units/kg and maintain ACT 200 sec</p> <p>Balloon angioplasty + abciximab + heparin as described in the stent + abciximab group</p>	<p>Death from any cause, MI, Urgent Target-vessel revascularization(UTVR) within 30 days of intervention</p> <p>(no measurements are given for primary endpoints)</p>	<p>Primary outcome: Stent + placebo 10.8% Stent + abciximab 5.3% (p<0.001) Angioplasty + abciximab 6.9% (p=.007)</p> <p>Major bleeding complications Stent + placebo 2.2% Stent + abciximab 1.5% Angioplasty + abciximab 1.4% (p=0.38)</p>
ESPRIT	<p>Placebo bolus + placebo infusion</p> <p>Eptifibatide 180mcg/kg bolus + 2mcg/kg/min infusion with an additional bolus of 180mcg/kg 10 min after the initial bolus. (pt with SCr >1.7 received 1mcg/kg/min)</p>	<p>Death, MI, UTVR, and thrombotic bailout with GP IIb/IIIa inhibitor within 48hrs after randomization</p> <p>MI defined as CK-MB 3x ULN in 2 samples for the first 24hrs after PCI. OR Clinical syndrome consistent with MI that included Q waves (at least 0.04 s) in 2 or more contiguous leads, or new left bundle branch block.</p>	<p>8% RR reduction of death or MI at 48hrs study was terminated early for efficacy</p>
TARGET	<p>Tirofiban 10mcg/kg bolus + 0.15mcg/kg/mins x 18-24hr + hep 70 units/kg to maintain ACT 250 sec</p> <p>Abciximab 0.25mg/kg + 0.125mcg/kg/min (max 10mcg/min) x 12hrs + hep as above</p>	<p>Death, MI, UTVR within 30days of procedure</p> <p>MI defined as MB 3 x ULN in 2 blood samples or by the finding of abnormal Q waves in 2 or more contiguous leads (measured at baseline and q6h x 24hrs after procedure).</p>	<p>Composite endpoints Tirofiban 7.6% Abciximab 6% (p=0.038) Death Tirofiban 0.5% Abciximab 0.4% (p=0.66) Nonfatal MI Tirofiban 6.9% Abciximab 5.4% (p=0.04) UTVR Tirofiban 0.8% Abciximab 0.7% (p=0.49)</p>
REPLACE II	<p>Bivalirudin 0.75mg/kg prior to start of intervention + infusion of 1.75mg/kg/hr for the duration of the procedure (provisional GP II/IIIa inhibitor)</p> <p>Heparin 65 units/kg (max of 7000 units) prior to PCI plus either abciximab 0.25mg/kg bolus and 0.125mcg/kg/min infusion (max of 10mcg/min) x 12hrs OR</p> <p>Heparin as described above plus eptifibatide 180mcg/kg x 2 boluses 10min apart and infusion at 2mcg/kg/min</p>	<p>Death from any cause, MI, UTVR, or in-hospital major bleeding</p> <p>MI defined by new Q waves in 2 or more contiguous leads or elevation in CK or CK-MB to 3x ULN within 2 days of revascularization or to 2 x ULN thereafter. (levels obtained in all pts Q8h x 24hrs after procedure)</p> <p>Major bleeding was defined as intracranial, intraocular, or retroperitoneal hemorrhage, clinically overt blood loss resulting in a decrease in Hgb of >3g/dl, any decrease in Hgb of >4g/dl or transfusion of 2 or more units of PRBC's or whole blood.</p>	<p>Primary endpoint Bivalirudin 9.2% Heparin 10% (p=0.32)</p> <p>In hospital major bleeding rates Bivalirudin 2.4% Heparin 4.1% (p<0.001)</p>
ISAR-REACT	<p>Clopidogrel 600mg + abciximab 0.25mg/kg and 0.125mcg/kg/min x 12hrs</p> <p>Clopidogrel 600mg + placebo bolus and infusion</p>	<p>Death from any cause, MI, UTVR owing to ischemia within 30 days after randomization.</p> <p>Diagnosis of MI was based on the development of pathologic Q waves in 2 or more contiguous leads or an elevation of CK or its MB isoenzyme to at least 3 x ULN in at least 2 blood samples.</p> <p>Large MI was based on the presence of pathologic Q waves in 2 or more contiguous leads or an elevation of CK or its MB isoenzyme to at least 5x ULN in at least 2 samples.</p>	<p>Primary endpoint Abciximab 4% Clopidogrel 4%</p>