REVIEW ARTICLE

Drugs 2009; 69 (1): 85-100
0012-6667/09/0001-0085/$55.55/0

Defining the Role of Platelet Glycoprotein Receptor Inhibitors in STEMI

Focus on Tirofiban

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Contents

Abstract

Tirofiban is a small molecule, nonpeptide tyrosine derivative. Although similar to abciximab in that it has a high specificity and affinity for the glycoprotein (GP) IIb/IIIa receptor, tirofiban dissociates from the GP IIb/IIIa receptor more rapidly than abciximab. Additionally, the action of tirofiban is reversed within hours after completion of the infusion, whereas abciximab binds irreversibly resulting in a considerably longer effect.

The efficacy of tirofiban in ST-segment elevation myocardial infarction (STEMI) has been demonstrated when administered in patients being managed with primary percutaneous coronary intervention (PCI). These trials primarily

studied tirofiban utilizing the high-dose bolus regimen (25 μg/kg bolus followed by a maintenance infusion of 0.15 μg/kg/min for 18–24 hours). The On-TIME (Ongoing Tirofiban in Myocardial Infarction Evaluation) 2 trial assessed early administration of the high-dose bolus regimen of tirofiban either at the referral centre or in the ambulance, in patients being transferred to a primary PCI centre. Early use of tirofiban resulted in both a significant increase in the rate of complete resolution of ST-segment deviation pre- and post-PCI, and improvement in clinical outcomes at 30 days.

Moreover, the multi-factorial MULTISTRATEGY (Multicentre Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction) trial, which compared the high-dose bolus regimen of tirofiban with standard dose administration of abciximab administered immediately prior to PCI, revealed similar effects on myocardial perfusion, ST-segment elevation recovery and clinical outcomes between the two agents, and confirmed the safety of tirofiban when used in combination with drug-eluting stents in patients with STEMI undergoing primary PCI.

These studies showed tirofiban to be a well tolerated and effective GP IIb/IIIa inhibitor. On the basis of the demonstrated benefits of the high-dose bolus regimen, tirofiban may be considered useful in the management of patients with STEMI.

1. ST-Segment Elevation Myocardial Infarction (STEMI)

ST-segment elevation myocardial infarction (STEMI) is precipitated by an acute obstruction in an epicardial artery leading to myocardial ischaemia, followed by myocardial necrosis and subsequent impairment in ventricular function.[1] Largely, this obstruction is precipitated by the formation of intra-arterial thrombus, resulting primarily from vascular injury caused by disruption of a high-risk or vulnerable plaque as a result of shear or mechanical stress. However, of potentially greater importance is the impaired blood flow within the microcirculation, which is evident in STEMI and related to reperfusion strategies. This is the manifestation of distal emboli and atherosclerotic plaque debris triggered by injury and thrombus formation within the infarct-related artery, which is also thought to be coupled with inflammation, vasospasm and endothelial dysfunction.[2,3] The impact on the microcirculation is quite apparent in patients in whom blood flow through the infarct-related artery is successfully restored, although myocardial perfusion is still impaired.[4]

Cell death is not immediate, with a significant percentage of myocardium being salvageable for several hours after the onset of symptoms.[5] Therefore, the goal of treatment for STEMI involves prompt and complete re-establishment of epicardial artery blood flow and myocardial perfusion.[6-8] The use of primary percutaneous coronary intervention (PCI) results in a significant reduction in the event rates for a number of outcome measures, including short-term mortality, non-fatal reinfarction and stroke, as well as the combined endpoint of death, non-fatal reinfarction and stroke.[9-13] On the basis of this and similar data, the guidelines put forth by the European Society of Cardiology (ESC) advocate that primary PCI is the ideal reperfusion strategy in STEMI.[14,15]

While primary PCI is the more effective strategy for treating STEMI, evidence supports its use in situations where the patient is ensured to be transferred to the catheterization laboratory within 90–120 minutes of presentation because delays have

been proven to have significant impact on measures of myocardial perfusion and clinical outcomes.[14-19]

2. Glycoprotein (GP) IIb/IIIa Inhibitors in Primary Percutaneous Coronary Intervention

2.1 The Central Role of Platelets in STEMI

Platelets play a central role in thrombus formation; therefore, inhibiting platelet function is essential for effective treatment of patients with STEMI undergoing primary PCI. Platelet aggregation is the final step in the development of a thrombus.[20]

Furthermore, the level of platelet activation is associated with clinical outcome in patients with STEMI. In a study of patients undergoing PCI,[21] higher levels of platelet reactivity were associated with a greater incidence of major adverse cardiac events (MACEs). Most recently, platelet reactivity was measured before and after treatment in a selected group of patients undergoing primary PCI assisted by systematic use of glycoprotein (GP) IIb/IIIa inhibitors.[22] Platelet reactivity, both at baseline and after bolus GP IIb/IIIa inhibitors, influenced the angiographic success of the procedure, as well as the degree of ST-segment resolution, the extent of myocardial necrosis, and the short- and mid-term clinical outcome in patients undergoing primary intervention.

This relationship may be critical because platelets may indeed comprise the majority of thrombus in STEMI. Platelets have been found to form the main constituent of thrombus aspirated from the epicardial arteries of patients with STEMI.[23]

2.2 GP IIb/IIIa Inhibitor Therapy

Recognition of the central role that platelet activation and aggregation has on myocardial perfusion and subsequent outcomes in STEMI has led to the recommended practice of utilizing dual antiplatelet therapy with aspirin and clopidogrel upon diagnosis of STEMI.[16]

The GP IIb/IIIa receptor is an important component of the platelet aggregation pathway. The GP IIb/IIIa receptor binds several substrates, most notably fibrinogen, which forms a bridge between platelets, directly mediating aggregation. GP IIb/IIIa is the most abundant glycoprotein on the platelet surface, although in the inactivated state, approximately 70% of GP IIb/IIIa complexes are distributed on the surface of the platelet, while the remaining receptors stay hidden.[24] Following platelet activation, the number of GP IIb/IIIa receptors on the cell surface increases exponentially.

GP IIb/IIIa inhibitors, which include abciximab, tirofiban and eptifibatide, selectively block the GP IIb/IIIa receptor on the surface of the platelet, thus preventing the binding of fibrinogen to the receptor, and have been regarded as the most potent inhibitors of platelet activity.[25] The first agent in this class that was introduced to clinical practice was abciximab, a chimaeric human-murine monoclonal antibody Fab fragment (c7E3).[25] Current practice of using GP IIb/IIIa inhibitors in the treatment of patients with STEMI undergoing PCI has been based primarily on the available evidence for abciximab because this agent has been the most widely studied.

In the ADMIRAL study (see table I for trial acronyms),[26] early administration of abciximab (often prior to entering the catheterization laboratory) was compared with placebo in 300 patients undergoing PCI with stenting for STEMI. At 30 days, 6.0% of patients in the abciximab group met the primary endpoint (a composite of death, reinfarction or urgent revascularization of the target vessel) versus 14.6% in the placebo group (odds ratio [OR] 0.41; 95% CI 0.18, 0.93; $p = 0.01$). These results were sustained at 6 months, with 7.4% and 15.9% (OR 0.46; 95% CI 0.22, 0.93; $p = 0.02$) of patients reaching the primary endpoint in the abciximab group and placebo groups, respectively. Additionally, there was a significantly higher rate of pre-procedural TIMI (Thrombolysis in Myocardial Infarction) grade 3 flow in the abciximab group than in the placebo group (16.8% vs 5.4%; $p = 0.01$).

In the CADILLAC trial,[27] utilizing a 2×2 factorial design, the strategies of balloon angioplasty (no stent) and stenting were compared, both alone and with concomitant administration of abciximab. Although the principle finding was

Table I. Clinical trial acronyms

Acronym	Definition
ACE	Abciximab and Carbostent Evaluation
ADMIRAL	Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-Up
BRAVE	Bavarian Reperfusion Alternatives Evaluation
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
FINESSE	Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events
HORIZONS-AMI	Harmonizing Outcomes with Revascularisation and Stents in Acute Myocardial Infarction
ISAR	Intracoronary Stenting and Antithrombotic Regimen
MULTISTRATEGY	Multicentre Evaluation of Single High-Dose Bolus Tirofiban vs. Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study
On-TIME	Ongoing Tirofiban in Myocardial Infarction Evaluation
STEEPLE	Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation
STRATEGY	Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs. Abciximab and Bare Metal Stent in Myocardial Infarction
TENACITY	Tirofiban Evaluation of Novel Dosing vs Abciximab with Clopidogrel and Inhibition of Thrombin

that stenting is the preferred strategy in patients with STEMI, there also appeared to be a benefit with the use of abciximab with respect to the composite endpoint of death, reinfarction, stroke and ischaemia-driven revascularization of the target vessel at both 30 days and 6 months. However, this effect was driven by an improvement in target vessel revascularization because there were no differences between the study arms in the rates of death, stroke or reinfarction when analysed individually.

Benefit, as it relates to long-term mortality, was established through the 400-patient ACE trial.[28,29] In this study, treatment with abciximab resulted in significant improvement in survival at 1 year compared with placebo (95% vs 88%; p = 0.017) in patients undergoing primary PCI with stenting. Unlike CADILLAC, patients were eligible for randomization only within 6 hours from onset of symptoms and treatment could be administered at the first medical contact.

A meta-analysis performed by De Luca and colleagues[30] evaluating the benefits of abciximab in patients with STEMI examined data from 11 randomized trials of abciximab in STEMI involving 27 115 patients. In patients undergoing primary PCI, abciximab was associated with a significant reduction in short-term (30 days) mortality (2.4% vs 3.4%; OR 0.68; 95% CI 0.47, 0.99; p = 0.047) and long-term (6–2 months) mortality (4.4% vs 2.0%; OR 0.69; 95% CI 0.52, 0.92; p = 0.01) in patients undergoing primary PCI. Use of abciximab was also linked to a significant reduction in 30-day reinfarction in primary PCI (1.0% vs 1.9%; OR 0.56; 95% CI 0.33, 0.94; p = 0.03).

Results from a separate meta-analysis also suggest a benefit of abciximab with regard to long-term clinical outcomes.[31] This analysis, which included 1101 patients from three studies evaluating GP IIb/IIIa inhibition with abciximab in primary PCI (ISAR-2, ADMIRAL and ACE), indicated a significant reduction in the estimated accumulated hazard rate of death or reinfarction at 3 years in patients receiving abciximab (12.9%) compared with those receiving placebo (19%) [relative risk (RR) 0.633; 95% CI 0.452, 0.887; p = 0.008]. Furthermore, a mortality benefit was also seen with the estimated accumulated hazard rate reduced with abciximab (10.9%) compared with placebo (14.3%) [RR 0.695; 95% CI 0.482, 1.003; p = 0.052].

3. Tirofiban

Tirofiban is a potent GP IIb/IIIa inhibitor, which has been well studied and used clinically in a variety of settings including STEMI and

non-ST-segment elevation acute coronary syndromes. Similar to abciximab, tirofiban is a competitive GP IIb/IIIa inhibitor with high specificity and affinity for the GP IIb/IIIa receptor.[32] Unlike abciximab, tirofiban is a small molecule, nonpeptide tyrosine derivative.[33] Tirofiban further differs from abciximab in that it dissociates from the GP IIb/IIIa receptor relatively rapidly, with a half-life of 2–4 hours, and its action is therefore reversed within hours after the completion of the infusion.[33] Abciximab binds irreversibly to the GP IIb/IIIa receptor, producing an effect that persists for the lifespan of the platelet.[25,34] Such reversibility may have significant implications with regard to bleeding, particularly in patients who have the need for emergent coronary artery bypass graft surgery.

4. Dose Administration of Tirofiban

The dose administration of tirofiban has evolved over time. It has been established that different dose administration regimens may be required based on the patient's diagnosis and the timing of PCI. A regimen utilizing a loading infusion of 0.4 μg/kg/min run over 30 minutes followed by a 0.10 μg/kg/min maintenance infusion has proven quite effective in the management of patients with non-ST-elevation acute coronary syndromes when administered at least 4 hours prior to PCI.[35-37] Studies conducted in similar patient populations who rather than receiving tirofiban prior to PCI were administered tirofiban immediately prior to PCI,[38,39] employed a dose administration regimen including a bolus of 10 μg/kg administered over 3 minutes followed by an infusion of 0.15 μg/kg/min. Given the benefit seen with the earlier dose administration regimen, it might be assumed that this dose would achieve adequate platelet inhibition, even when administered immediately prior to initiation of PCI. Yet, results of such studies were not as favourable for tirofiban, revealing an increase in clinical events compared with abciximab.[39] Follow-up studies have suggested that a higher incidence of myocardial infarction (MI) after PCI seen in these studies was likely to be a result of suboptimal platelet inhibition from 15–60 minutes following the onset of treatment.[40] These studies also indicated that this suboptimal platelet inhibition could be overcome by a regimen including a higher bolus dose of tirofiban (25 μg/kg) and revealed that a high-dose bolus of tirofiban results in a level of platelet inhibition[41] necessary for coronary intervention.[21] Therefore, a regimen using a 25 μg/kg bolus dose of tirofiban followed by a maintenance infusion of 0.15 μg/kg/min (high-dose bolus regimen) is considered more appropriate when administration immediately prior to PCI is warranted.

Similarly, a high-dose bolus regimen of tirofiban may potentially induce a potent affect on platelets compared with abciximab. When platelet inhibition was compared in 112 STEMI patients who were either administered the standard dose of abciximab or one of two doses of tirofiban (10 μg/kg bolus or the high-dose bolus regimen), mean periprocedural platelet inhibition exceeding 80% was only seen with the high-dose tirofiban regimen.[42] A separate study involving 66 patients with STEMI undergoing PCI provided comparable results.[43] The high-dose bolus regimen of tirofiban produced significantly higher levels of platelet inhibition than abciximab when measured immediately (30 minutes), 60 minutes and 120 minutes after PCI. Given its similar effect on platelet function to abciximab, tirofiban, administered using the high-dose bolus regimen, may indeed be considered a beneficial cost-effective alternative to abciximab in patients with STEMI undergoing primary PCI.[42]

5. Tirofiban in STEMI

The utility of tirofiban in patients with STEMI has been investigated in several trials[42-56] (table II). These studies have included assessment of both the 10 μg/kg bolus and high-dose bolus regimens. Furthermore, the effects of tirofiban were analysed when administered early as well as immediately prior to primary PCI.

5.1 Rationale for Early Administration of Tirofiban

In situations where a patient presents to an institution without the capability to perform primary

PCI, the decision needs to be made whether to immediately administer thrombolysis or to transfer the patient to a primary PCI centre. A growing body of evidence supports the practice of transferring these patients. A meta-analysis of six clinical trials, including 3750 patients comparing on-site thrombolysis with transfer for PCI,[57] revealed a significant reduction in the combined criteria of death, reinfarction and stroke in patients who were transferred for PCI (42%; 95% CI 29, 53; $p < 0.001$). Additionally, transfer resulted in a 68% reduction in reinfarction (95% CI 34, 84; $p < 0.001$) and a 56% reduction in stroke (95% CI 15, 77; $p = 0.015$).

It makes strong clinical sense to initiate myocardial reperfusion using a highly effective antiplatelet agent as soon as possible after symptom onset, particularly in those patients being transferred for primary PCI.[58] Early use of GP IIb/IIIa inhibitors has been associated with improvement in post-procedural myocardial perfusion and reduction in clinical parameters (death or cardiogenic shock).[59,60]

An important measure of myocardial perfusion is ST-segment resolution. Level of ST-segment resolution indicates infarct size, with larger infarct sizes found in patients with no or incomplete ST-segment resolution. Moreover, the strength of the prognostic ability of ST-segment resolution has been demonstrated in a number of studies and it is an independent predictor of improvement in left ventricular function as well as reduction in early and late clinical events.[61-64] A meta-analysis of 11 trials performed by De Luca and colleagues,[59] which included individual data from 1662 STEMI patients undergoing PCI, compared pre-procedural GP IIb/IIIa inhibitor use with GP IIb/IIIa inhibitors administered in the catheterization laboratory. Pre-PCI administration of a GP IIb/IIIa inhibitor was associated with a significantly higher rate of ST-segment resolution (60.3% vs 54.1%; $p = 0.02$). Although mortality was not significantly different between groups (3.7% vs 4.7%; hazard ratio [HR] 0.78; 95% CI 0.49, 1.26; $p = 0.3$), improved survival was demonstrated with early administration of abciximab compared with late administration (2.6% vs 6.5%; HR 0.39; 95% CI 0.17, 0.9; $p = 0.026$).

5.2 Data from Trials on Early Administration of Tirofiban: 10 μg/kg Bolus Regimen

Results from trials employing early administration of tirofiban in patients undergoing primary PCI utilizing the 10 μg/kg bolus regimen have implied a potential benefit through the ability of tirofiban to restore infarct artery blood flow and myocardial perfusion, although no improvement was seen in clinical outcomes.[44-48,51]

5.3 Early Administration of Tirofiban: High-Dose Bolus Regimen

The On-TIME 2 trial,[54-56] a placebo-controlled, multicentre, international, randomized trial involving 984 patients with STEMI diagnosed in the ambulance or at a referral centre, was the first study to determine the benefits of pre-hospital administration of tirofiban at the high-dose bolus regimen in addition to dual antiplatelet therapy measured by ST-segment deviation resolution. Treatment was initiated in the ambulance or at the referral centre, and all patients received aspirin 500 mg, a high loading dose of clopidogrel (600 mg), heparin 5000 IU, and either high-dose bolus regimen tirofiban or placebo. Study drug was initiated at a median of 76 minutes after symptom onset and 55 minutes prior to angiography/PCI. Figure 1 summarizes the cumulative residual ST-segment deviation over the period of time from diagnosis until 60 minutes post-PCI. At the time of arrival to the PCI centre, patients treated with tirofiban had significantly lower cumulative residual ST-segment deviation than those who received placebo (10.9 ± 9.2 mm vs 12.1 ± 9.4 mm; $p = 0.028$).[55] Moreover, ST-segment resolution prior to PCI occurred significantly more often in the tirofiban arm ($p = 0.041$ for trend). The cumulative residual ST-segment deviation 1 hour post-PCI (primary endpoint) was 3.6 ± 4.6 mm for the tirofiban group versus 4.8 ± 6.3 mm in the placebo group ($p = 0.003$). Additionally, the percentage of patients with more than 3 mm residual ST-segment deviation was significantly lower in the tirofiban than the placebo arm (36.6% vs 44.3%; $p = 0.026$). At 30 days, results demonstrated a significant benefit favouring tirofiban with regard to the

Table II. Summary of studies of tirofiban in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention (PCI) with stents

Study	Period	Study design (no. of patients)	Dose	Symptom duration (h)	Primary endpoints
Cutlip et al.[44]	2001–2	Early (n = 28) vs late or no (n = 30) tirofiban	10 μg/kg bolus over 3 min → 0.15 μg/kg/min infusion	<12	Pre-procedural TIMI flow grade
TIGER-PA[45]	1999–2001	Early (n = 50) vs late (n = 50) tirofiban	10 μg/kg bolus over 3 min → 0.15 μg/kg/min infusion	<12	Pre-procedural TIMI flow grade, cTFC and TMPG
On-TIME[46]	2001–2	Early (n = 251) vs late (n = 256) tirofiban	10 μg/kg bolus over 3 min → 0.15 μg/kg/min infusion	<6	Pre-procedural TIMI flow grade
De Luca et al.[47]	1997–2002	Observational study of tirofiban (n = 481) vs no tirofiban (n = 1488)	10 μg/kg bolus over 3 min → 0.15 μg/kg/min infusion	<12/12–24[a]	Post-procedural TIMI flow grade, distal embolization, TMPG
Emre et al.[48]	2002–3	Early (n = 32) vs late (n = 34) tirofiban	10 μg/kg bolus over 3 min → 0.15 μg/kg/min infusion	<6	Myocardial perfusion/ functional recovery at 30 d
Ernst et al.[42]	2002–3	Comparison of platelet inhibition in 3 GP IIb/IIIa inhibitor regimens (n = 112)	10 μg/kg bolus regimen vs 25 μg/kg bolus regimen (both → 0.15 μg/kg/min infusion)	<6	Platelet inhibition at 3 different timepoints after PCI
STRATEGY[49]	2003–4	Tirofiban + DES (n = 87) vs abciximab + BMS (n = 88)	25 μg/kg bolus over 3 min → 0.15 μg/kg/min infusion	<12/12–24[a]	Composite of death, nonfatal MI stroke, or binary restenosis at 8 mo
Danzi et al.[50]	2004	Tirofiban (n = 50) vs abciximab(n = 50)	25 μg/kg bolus over 3 min → 0.15 μg/kg/min infusion	<6	Recovery of left ventricular function
Shen et al.[51]	2005–6	Early (n = 57) vs late tirofiban (n = 57)	10 μg/kg bolus regimen vs 25 μg/kg bolus regimen (both → 0.15 μg/kg/min infusion)	<12	MACE at 30 d and 6 mo
Van Werkum et al.[43]	2005–6	Comparison of platelet inhibition in 3 GP IIb/IIIa inhibitor regimens (n = 60)	25 μg/kg bolus → 0.15 μg/kg/ min infusion	<6	Platelet inhibition at 3 different timepoints after PCI
Fu et al.[52]	2005–7	Tirofiban (n = 72) vs placebo (n = 78)	10 μg/kg bolus over 3 min → 0.15 μg/kg/min infusion	<12	Pre-/post-procedural TIMI flow grade, myocardial perfusion, platelet aggregation, CPK, CPK-MB; MACE at 6 mo
MULTI-STRATEGY[53]	2004–7	Tirofiban (n = 372) vs abciximab (n = 372) + either DES or BMS	25 μg/kg bolus over 3 min → 0.15 μg/kg/min infusion	<12/12–24[a]	50% ST-segment elevation resolution at 90 min post-PCI
On-TIME 2[54-56]	2006–7	Early tirofiban (n = 491) vs placebo (n = 493)	25 μg/kg bolus over 3 min → 0.15 μg/kg/min infusion	<24	Residual ST-segment deviation 1 h after PCI

a <12 h, also inclusion between 12 and 24 h in case of continuing ischemia.

BMS = bare metal stent; **CPK** = creatine phosphokinase; **CPK-MB** = CPK isoenzyme MB; **cTFC** = corrected TIMI frame counts; **DES** = drug-eluting stent; **MACE** = major adverse cardiac events; **MI** = myocardial infarction; **TIMI** = Thrombolysis in Myocardial Infarction; **TMPG** = TIMI myocardial perfusion grade; → indicates followed by.

combined incidence of death, recurrent MI, urgent target vessel revascularization (TVR) or thrombotic bailout (tirofiban 26.0% vs placebo 32.9%; p = 0.020). Further analysis suggested a link between the level of residual ST-segment deviation and mortality.[55] Patients with <3 mm residual ST-segment deviation had a significantly lower mortality rate than those with ≥3 mm (0.6% vs 4.1%; p < 0.001) [figure 2].

Similar to the effects of early administration of abciximab in the ADMIRAL trial, On-TIME 2 demonstrated a benefit of the tirofiban high-dose bolus regimen compared with placebo with respect to clinical outcomes.

6. Head-To-Head Comparison of Tirofiban High-Dose Bolus Regimen and Abciximab

As stated in section 4, smaller studies suggested similarities pertaining to inhibition of platelet reactivity between tirofiban, when administered

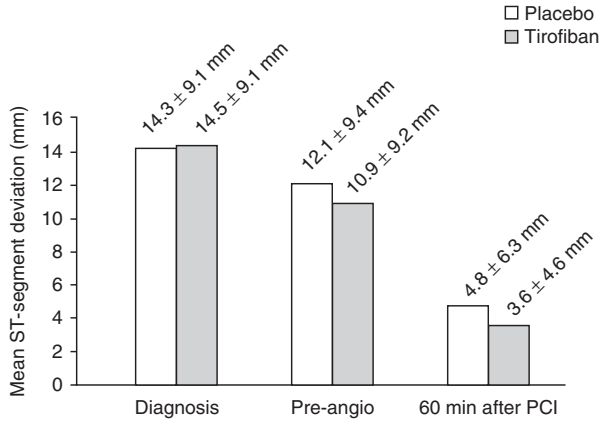


Fig. 1. Cumulative ST-segment deviation over time. The mean (±SD) ST-segment deviation is measured at diagnosis, immediately prior to angiography (pre-angio) and at 60 minutes after percutaneous coronary intervention (PCI).

at the high-dose bolus regimen, and abciximab.[42,43] Results from subsequent trials in patients with STEMI have shown the high-dose bolus regimen of tirofiban to be comparable with abciximab with respect to clinical outcomes. Danzi and colleagues[50] demonstrated that not only were the rates of TIMI 3 grade flow at the completion of the procedure similar to that of abciximab, but also that comparable rates of 30-day recovery of left ventricular function were seen in patients receiving tirofiban using the high-dose bolus regimen. The STRATEGY trial was conducted with the purpose of evaluating tirofiban as a more cost-effective approach to primary PCI.[49] The STRATEGY study confirmed the efficacy of tirofiban in the setting of primary PCI when compared with abciximab. These results were recently extended for up to 2 years of follow-up.[65] The MULTISTRATEGY was the largest comparison of tirofiban with abciximab in the setting of primary PCI.[53]

Utilizing a 2×2 factorial open-label design, MULTISTRATEGY compared tirofiban versus abciximab, bare metal stent (BMS) versus drug-eluting stent (DES) [in the form of a sirolimus stent], and the interaction between the two treatments (GP IIb/IIIa inhibitor and stent). 745 patients were enrolled from 16 centres and randomized to either tirofiban plus sirolimus stent, tirofiban plus BMS, abciximab plus sirolimus stent or abciximab plus BMS. The majority of patients received triple antiplatelet therapy with aspirin and clopidogrel (300–600 mg) in addition to the GP IIb/IIIa inhibitor therapy.

Tirofiban was observed to be non-inferior to abciximab with regard to the primary endpoint of ST-segment resolution at 90 minutes post-procedure. At least 50% of ST-segment resolution occurred in 85.3% and 83.6% of patients in the tirofiban and abciximab arms, respectively (RR 1.02; 95% CI 0.958, 1.086; $p < 0.001$ for non-inferiority). Furthermore, no interaction occurred between the different GP IIb/IIIa inhibitors and stent types ($p = 0.60$). At 8 months (figure 3), the rate of MACE was similar between patients who received tirofiban and those receiving abciximab (9.9% vs 12.4%; $p = 0.30$), although significantly

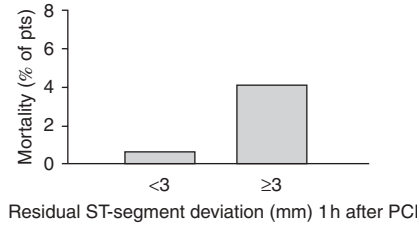


Fig. 2. Mortality at 30 days by residual ST-segment deviation in all patients (pts) receiving tirofiban or placebo. The rate of mortality measured as percentage of pts based on the level of ST-segment deviation.

lower with the use of DES than BMS (7.8% vs 14.5%; p = 0.004). However, at no timepoint were any interactions evident between the different GP IIb/IIIa inhibitors and stent types (p = 0.95). Additionally, no significant differences in stent thrombosis were noted between the four study arms.

7. Adverse Events

It is to be expected that an agent that suppresses platelet function would be associated with an increase in the risk of bleeding compared with placebo. As it is well known that bleeding complications in patients undergoing PCI have been associated with an increased morbidity and mortality risk,[66] preventing excessive bleeding is critical. Although it has been suggested that early initiation of a GP IIb/IIIa inhibitor in patients with acute coronary syndromes managed with PCI may lead to increased in bleeding,[67] this phenomenon was not evident in either the On-TIME 1 or On-TIME 2 studies. On-TIME 2 showed that there was no excess in major bleeding, even in patients receiving pre-hospital high-dose bolus tirofiban in addition to high-dose clopidogrel (4.0% vs 2.9%; p = 0.363).[56]

When compared directly against abciximab, major and minor bleeding is overall numerically lower with high-dose bolus tirofiban administered immediately prior to PCI, but this difference is not statistically significant.[49,50,53]

There has been growing interest in alternatives to GP IIb/IIIa inhibitors, namely bivalirudin. In the HORIZONS-AMI trial, when compared with unfractionated heparin plus planned GP IIb/IIIa inhibitor therapy, bivalirudin monotherapy was associated with a similar rate of net adverse clinical events (MACE plus bleeding) but a significant reduction in major bleeding (8.3% vs 4.9%; RR 0.60; 95% CI 0.46, 0.77; p < 0.001).[68] However, it is important to recognize that the rate of TIMI grade major bleeding in patients receiving unfractionated heparin plus planned GP IIb/IIIa inhibitor in HORIZONS-AMI (5%) was relatively high compared with that seen in On-TIME 2 (4%).[56]

Although abciximab has been associated with an increase in thrombocytopenia,[69] this is not evident in all drugs within the GP IIb/IIIa inhibitor class. In both the STRATEGY and MULTISTRATEGY studies, abciximab was associated with a significantly higher rate of thrombocytopenia than tirofiban.[49,53] Moreover, in On-TIME 2, the overall incidence of thrombocytopenia was very low, with no significant increase seen in patients receiving pre-hospital tirofiban.[56]

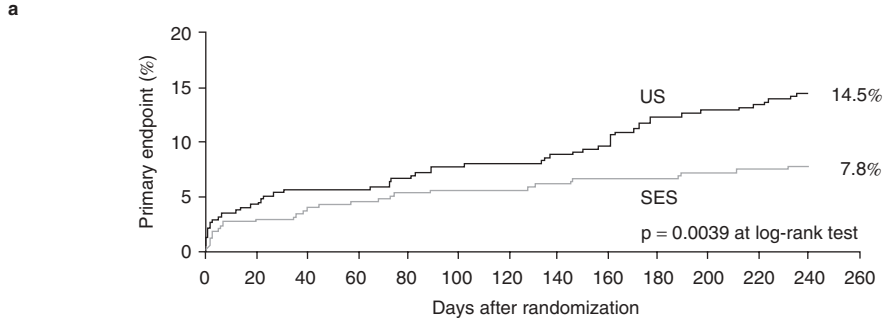
8. GP IIb/IIIa Inhibitors in STEMI: Practical Considerations

A multitude of studies demonstrate the value of GP IIb/IIIa inhibitor therapy and specifically tirofiban in the management of patients with STEMI. However, in practice, there continues to remain a lack of clarity with regard to the practical aspects of these agents. These include who should receive these agents, when they should be initiated, duration of therapy and ideal concomitant agents. This section is designed to address such issues.

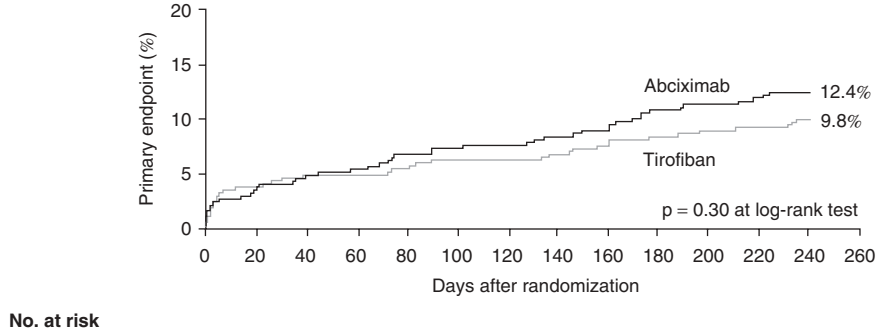
8.1 Candidates for GP IIb/IIIa Inhibitors

The guidelines put forth by the American College of Cardiology/American Heart Association and the ESC designate the use of GP IIb/IIIa inhibitors as a class IIa indication.[14-16] Taking into consideration these recommendations along with available evidence, it is reasonable for the vast majority of patients with STEMI being managed with primary PCI to receive GP IIb/IIIa inhibitor therapy. Results from On-TIME 2 confirm that the practice of reserving these agents for only those patients with large thrombus burden or requiring bailout is not optimal, as this particular strategy was used in the control arm. As stated in section 5.1, patients who received early administration of tirofiban yielded a significantly greater benefit with regard to post-procedural myocardial perfusion.[56]

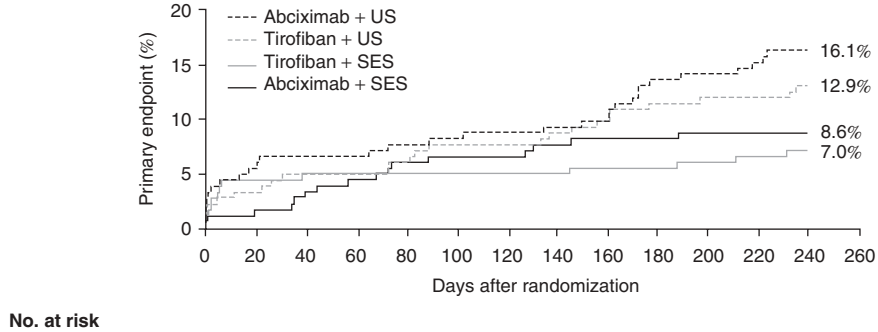
The small minority of patients for whom GP IIb/IIIa inhibitor therapy may not be appropriate includes those at a considerably high risk



No. at risk					
US	372	351	342	326	318
SES	372	355	351	347	343



No. at risk					
Abciximab	372	351	343	331	325
Tirofiban	372	355	350	342	336



No. at risk					
Abciximab + US	186	174	170	161	156
Tirofiban + US	186	177	172	165	162
Abciximab + SES	186	178	174	171	170
Tirofiban + SES	186	177	177	176	173

Fig. 3. Cumulative Kaplan-Meier estimates of the rates of the primary endpoints during follow-up period. Cumulative risk of events at 240 days for the primary endpoint, consisting of the composite of overall mortality, reinfarction and reintervention in the target vessel. Comparisons shown are for (**a**) uncoated stent (US) vs sirolimus stent (SES); (**b**) abciximab vs tirofiban; and (**c**) all four groups (abciximab and US, tirofiban and US, abciximab and SES, and tirofiban and SES) [reproduced from Valgimigli et al.,[53] © 2008, American Medical Association. All rights reserved].

of bleeding as well as those who present later than 6 hours after symptom onset. However, data such as that from the BRAVE 3 or CADILLAC studies have suggested that patients in whom a significant amount of time has elapsed between symptom onset and GP IIb/IIIa inhibitor administration may not yield benefit from these agents.[27,70] The BRAVE 3 investigators concluded that abciximab initiated in the catheterization laboratory did not improve outcomes in patients already pre-loaded with clopidogrel 600 mg. These results conflict with On-TIME 2, where there was a significant benefit with GP IIb/IIIa inhibition administered in addition to high-dose clopidogrel. The fundamental reason for this difference may have been the fact that in BRAVE 3 and CADILLAC studies, the median time from symptom onset to study drug initiation was 2 hours compared with 76 minutes in On-TIME 2. Although speculative, this may imply that there is loss of benefit with GP IIb/IIIa inhibitors when the time from symptom onset to presentation exceeds 6 hours. This is largely consistent with the knowledge that beyond 4–5 hours from onset of symptoms, there is little myocardium to be salvaged. Thus, microcirculatory restoration may become less critically important at this later stage.

8.2 Optimal Timing of Therapy

Therefore, the time of administration is ideally as early after onset of symptoms as possible. With respect to clinical parameters, in an analysis of the FINESSE trial[60] in which 2452 patients with STEMI were randomized to primary PCI, facilitated PCI with abciximab, or facilitated PCI with abciximab plus reteplase, there was a non-significant, yet profound, reduction in the incidence of cardiogenic shock at 90 days in patients receiving early abciximab compared with those who received it in the catheterization laboratory, specifically those who were randomized to treatment within 3 hours after symptom onset (4.7% vs 7.7%; $p = 0.052$). There was no difference between the study arms in patients presenting >3 hours after symptom onset.

In addition, a prespecified pooled analysis of the two On-TIME 2 study phases (open-label and double-blind phases), comprising a total of 1398 patients was performed. This analysis was powered to detect a 40% relative reduction in major adverse cardiac events at 30 days. Results of this analysis showed a borderline significant reduction in mortality with the use of pre-hospital tirofiban compared with placebo or no tirofiban (2.2% vs 4.1%; $p = 0.051$). Furthermore, there as a significant reduction in the combined incidence of death/re-MI/urgent TVR/stroke/major bleeding (net clinical outcome) with the use of pre-hospital tirofiban (8.0%) compared with placebo or no tirofiban (11.6%) [$p = 0.024$]. This effect was most apparent in patients who received tirofiban shortly (within 75 minutes) after the onset of symptoms.[71]

8.3 Duration of Therapy

At this time, there is no consensus on an optimal duration of therapy for GP IIb/IIIa inhibitors. However, recently published data from Thiele and colleagues[72] suggested that an intracoronary bolus of a GP IIb/IIIa inhibitor with no infusion may be optimal compared with standard dose administration, which includes a 12-hour infusion. In a study of 154 patients undergoing primary PCI, intracoronary abciximab resulted in a smaller median infarct size than the standard regimen (15.1% vs 23.4%, respectively; $p = 0.01$), as well as a smaller extent of microvascular obstruction ($p = 0.01$) and significantly improved myocardial perfusion measured as early ST-segment resolution (77.8% vs 70.0%, respectively; $p = 0.006$). There was also a trend towards a lower major adverse cardiac event rate after intracoronary versus standard abciximab (5.2% vs 15.6%; RR 0.33; 95% CI 0.09, 1.05; $p = 0.06$). These data suggest that future administration of GP IIb/IIIa inhibitors may be focused on the method of administration rather than duration of infusion.

8.4 Optimal Concomitant Therapy

If possible, GP IIb/IIIa inhibitor therapy should always be administered in conjunction

with aspirin (preferably intravenously), high-dose clopidogrel and a restricted dose of unfractionated heparin. In order to reduce the risk of bleeding, no additional unfractionated heparin should be administered in the catheterization laboratory when the activated clotting time is >200 seconds. Alternatively, low-dose enoxaparin (0.75 mg/kg) may also be considered. Results from the STEEPLE trial[73] noted that lowering the dose of enoxaparin reduced bleeding without compromising efficacy. Although this study included patients undergoing elective PCI, it may be speculated that these results could apply to primary PCI.

8.5 Surveillance

No particular surveillance is necessary when administering GP IIb/IIIa inhibitor therapy nor is there any evidence supporting dose adjustment during the maintenance infusion, although patients with renal insufficiency should continually be monitored for bleeding. An analysis of the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) registry[74] observed that patients with renal insufficiency were more likely to experience GP IIb/IIIa inhibitor overdose resulting in an increase in bleeding complications. However, these data are based mainly on eptifibatide, therefore it is not clear if these results apply to tirofiban. Still, in cases of severe renal insufficiency (creatinine clearance <30 mL/min for tirofiban and <50 mL/min for eptifibatide),[75,76] reducing the dose of GP IIb/IIIa inhibitor therapy may be considered in order to maintain efficacy while preventing excess bleeding in these patients.

9. The Future of GP IIb/IIIa Inhibitors in STEMI

In general, the value of tirofiban and GP IIb/IIIa inhibition in the management of patients with STEMI has been supported through a wealth of evidence. The future of these agents is likely to be shaped by emerging data and new recommendations regarding combination therapy and approaches to the general management of STEMI. For example, with the recent adjustment in the STEMI guidelines,[15] which clearly state that pre-hospital infarct diagnosis and therapy is a class I indication, more studies should focus on the effect of antithrombotic/antiplatelet treatment initiated in the ambulance.

With respect to combination therapy, provocative data from the TENACITY study[77] implies that a strategy of bivalirudin plus high-dose bolus tirofiban may not only improve ischaemic outcomes to a greater extent than those seen in the HORIZONS-AMI study, but also reduce the rate of bleeding. Data from the 383 patients with acute coronary syndrome undergoing PCI indicate a profound reduction in the composite endpoint of 30-day death/MI/urgent TVR/major bleeding with the combination of high-dose bolus tirofiban plus bivalirudin (5.6%) compared with the combinations of abciximab plus heparin (9.1%), high-dose bolus tirofiban plus heparin (10.1%) and abciximab plus bivalirudin (10.5%).

The use of the radial approach for PCI in patients administered GP IIb/IIIa inhibitors may also further minimize bleeding. In an analysis of three separate registries including 32 822 patients comparing radial with femoral access, the transfusion rate in patients undergoing PCI using the radial approach was half of that seen in patients undergoing femoral PCI.[78] Furthermore, the adjusted mortality rate at 30 days and 1 year was significantly reduced with the use of radial PCI (30 days: OR 0.71 [95% CI 0.61, 0.82]; 1 year: OR 0.83 [95% CI 0.71, 0.98]; all $p < 0.001$). Future studies should evaluate the potential for a strategy employing tirofiban, unfractionated heparin and clopidogrel using radial access and how that may compare with bivalirudin plus clopidogrel using the femoral approach, with regard to ischaemic outcomes and bleeding complications.

Another strategy that warrants additional research is the role of GP IIb/IIIa inhibitors administered as an intracoronary bolus without infusion because preliminary studies of both abciximab and tirofiban have suggested the

possibility of improved efficacy with similar or less bleeding.[79]

10. Conclusions

Although earlier issues related to dose administration have questioned the role of tirofiban in PCI,[38,39] more recent studies involving the high-dose bolus regimen support its efficacy in patients with STEMI undergoing primary PCI.[49,50,53,56] On-TIME 2 established improvement in myocardial perfusion with pre-hospital administration of high-dose bolus tirofiban and, unlike the trials of lower-dose bolus regimens,[44-48,51] these results may translate to clinical benefit, while not significantly increasing bleeding complications.

Direct comparison with abciximab has shown the high-dose bolus regimen of tirofiban to significantly improve platelet inhibition.[42] Furthermore, other studies, including the MULTISTRATEGY trial, suggest that the high-dose bolus regimen of tirofiban may be as efficacious as abciximab, while resulting in a numerically lower incidence of bleeding complications and significantly lower incidences of thrombocytopenia.[49,53] The efficacy and safety profile of the high-dose bolus regimen lends itself to the opportunity for future research to further confirm the role of tirofiban in the management of patients with STEMI.

Acknowledgments

The authors would like to acknowledge Melissa Hammond (Snowfish, LLC Great Falls, VA, USA) for her editorial assistance on this review and Iroko Cardio LLC for their unrestricted grant to support Ms Hammond. The authors received no financial support for their work on this review.

Dr van 't Hof has received a research grant from Merck, and Dr Valgimigli has received speaker's bureau and research grants from Merck and Iroko Cardio LLC.

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