TIROFIBAN (GLYCOPROTEIN IIB/IIIA INHIBITOR) IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION UNDERGOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION

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ABSTRACT

Introduction:

Primary percutaneous coronary intervention (PCI) is the preferred method for early restoration of blood flow in the infarct-related vessel in patients with ST-segment elevation myocardial infarction (STEMI), and adjunctive anti-platelet therapy is found to be associated with clinical outcomes following primary PCI. Glycoprotein IIb/IIIa inhibitors (GPI) act by inhibiting the final common pathway of platelet aggregation, and play an important role in the management of acute STEMI. Tirofiban is a small molecule, non-peptide tyrosine derivative which belongs to the class of glycoprotein IIb/IIIa inhibitors.

Aims:

This review assesses the evidence for therapeutic value of tirofiban as a Gp IIb/IIIa inhibitor in patients with ST-segment elevation myocardial infarction undergoing PCI.

Evidence review:

Several large, randomized controlled trials show that tirofiban as adjunctive therapy to standard care in patients with ST-segment elevation myocardial infarction undergoing PCI is associated with a significant reduction in the incidence of death or major adverse cardiovascular events (MACE). Data suggests that increasing the tirofiban bolus dose from 10 to 25 μg/kg is necessary to obtain an optimal level of platelet inhibition and is similar to that of other GPI. Data also suggests that intracoronary infusion is superior than intravenous infusion in the situation of no- or slow-reflow. Tirofiban was well tolerated in most of the trials.
Bleeding is the most common side effect but the incidence of life-threatening bleeding associated with the GP IIb/IIIa antagonists has been reported to be as low as <0.2%.

Methods:

English language literature searches were conducted in various World Wide Web, search engines like Google and PubMed. Some important selected articles were analyzed and a study was performed.

Conclusion:

Tirofiban has gained widespread acceptance as an adjunct to standard anticoagulation therapy in patients with STEMI undergoing PCI, and may be particularly useful when given early in high bolus dose and intracoronary infusion for no- or slow-reflow.

Keywords: Tirofiban, glycoprotein iia/iib inhibitors, ST-segment elevation myocardial infarction, primary percutaneous coronary intervention, abciximab, intracoronary

Objective:

Tirofiban is a small molecule, non-peptide tyrosine derivative which belongs to the class of glycoprotein IIb/IIia inhibitors. This review summarizes the effects of tirofiban infusion on angiographic measures, ST-segment resolution, and clinical outcomes in patients with ST-segment elevation Myocardial Infarction undergoing primary percutaneous coronary intervention.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is the preferred method for early restoration of blood flow in the infarct-related vessel in patients with ST-segment elevation myocardial infarction (STEMI) (1-3), and adjunctive anti-platelet therapy is found to be associated with clinical outcomes following primary PCI (4, 5). In addition to the standard dual antiplatelet therapy consisting of aspirin and clopidogrel, further measures to inhibit platelet aggregation, such as addition of a glycoprotein IIb/IIia inhibitor (GPI), have been shown to reduce thrombotic complications and the composite incidence of death, myocardial infarction, and the need for target vessel revascularization after PCI.

Platelets play central role in thrombotic events in acute coronary syndromes (ACS) and during percutaneous coronary interventions (PCI). Platelet activation occurs through various mechanisms and all culminate in expression of the surface GP IIb-IIIa receptors which mediate their aggregation and thrombosis. GPI remain the most powerful antiplatelet agents by inhibiting this final common pathway of platelet activation. The role of GPI in the treatment of coronary ischemic events has evolved through the past 20 years. Given their potent antiplatelet activity and consistent anti-ischemic benefit in major trials, they
were an integral part of antiplatelet-antithrombin portfolio in the treatment of ACS and during PCI over a decade (6).

**METHODS**

English language literature searches were conducted in various World Wide Web, search engines like Google and PubMed using the following keywords: “tirofiban”, “glycoprotein iiib/iia inhibitors”, “primary percutaneous coronary intervention”, “acute ST-elevation myocardial infarction”, “intracoronary”, “no-reflow’ and “randomized control trial”. Some important selected articles were analyzed and a study was performed.

**DISCUSSION AND RESULT**

**Glycoprotein iib/iia inhibitor:**

Platelet aggregation plays an important role in the formation of embolization. Glycoprotein IIb/IIIa inhibitors (GPI) block the final pathway of platelet aggregation, combine with the glycoprotein IIb/IIIa receptors selectively and inhibit the thrombinogen I competitively. And also, GPI could inhibit the activation, adhesion and aggregation of platelet. The pharmacological mechanisms of GPI were contributed to the formation of platelet thrombi, restoration the antegrade coronary flow of occlusive vessel and reducing the incidence of the ischemia event. From the recent researches, GPI has its obvious advantages in inhibiting the formation of platelet thrombus, but bleeding event was the main complication (7).

In a recent meta-analysis, GPI use was associated with a 62% reduction in 30-day re-infarction, a 42% reduction in 30-day repeat PCI, a 53% reduction in short-term mortality, and a 62% reduction in long-term mortality, with a non-significant increase in major bleeding(8).

Several GpIIb/IIIa inhibitors exist: abciximab (ReoPro), eptifibatide (Integrilin), tirofiban (Aggrastat), roxifiban, orbofiban. Three (abciximab, eptifibatide, and tirofiban) are licensed for human use.

Abciximab, a human-murine chimeric Fab fragment of a monoclonal antibody against the Gp IIb/IIIa receptor, was the first agent of this class to demonstrate clinical effectiveness. The molecular weight of abciximab is 47615 daltons. Eptifibatide is a synthetic cyclic heptapeptide with a molecular weight of 800 daltons, whereas tirofiban is a nonpeptide with a molecular weight of 495 daltons.

It takes about 4 hours to restoration of normal platelet aggregation after end of infusion of eptifibatide or tirofiban. Abciximab, on the other hand, binds much more avidly to the Gp IIb/IIIa receptor than the other two agents and has a measurable antiplatelet activity for several days (72 hours)(9).

**Tirofiban:**

Tirofiban is a small molecule, non-peptide tyrosine derivative which belongs to the class of glycoprotein IIb/IIIa inhibitors (GPI). By preventing the binding of fibrinogen and von Willebrand factor to the GP IIb/IIIa receptor on the surface of the platelet, GPIs are currently regarded as the most potent
inhibitors of platelet aggregation.

Though similar to abciximab in that it has a high affinity for the GP IIb/IIIa receptor, tirofiban dissociates from the GP IIb/IIIa receptor more rapidly than abciximab (10, 11). Its anti-aggregatory effects reverse within hours after the completion of the infusion, whereas abciximab binds near irreversibly to the receptor resulting in a considerably longer effect(10, 12). Additionally, tirofiban does not inhibit other b3 integrins, such as the vitronectin receptor, at the surface of vascular cells or the activated MAC-1 receptor on leucocytes(13), which have been traditionally regarded as crucial targets to explain abciximab effects on microcirculation(14).

Marco Valgimigli et al. analysis showed that adjunctive tirofiban therapy, compared with placebo, is associated with a >30% reduction in all considered ischaemic endpoints including overall mortality, mortality or MI( Myocardial Infarction), and MACE( Major Adverse Cardiovascular Events) rates within 30 days after treatment. In absolute terms, tirofiban administration in 40 patients would prevent one death or MI, whereas 100 treated patients would lead to one fatal event prevention. Importantly, the benefit observed soon after intervention persisted at longest available follow-up. Interestingly, the magnitude of benefit for mortality observed in their analysis for tirofiban was quite similar to the treatment benefit shown by abciximab in a recent meta-analysis(15).

**Dosing regimen:**

Tirofiban is a small, nonpeptide molecule, with a short half-life and marked specificity for the glycoprotein IIb/IIIa receptor.

**STRATEGY (Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs Abciximab and Bare Metal Stent in Myocardial Infarction)** Investigators explained that subsequent dose-ranging studies showed that increasing the tirofiban bolus dose from 10 to 25 μg/kg was necessary to obtain an optimal level of platelet inhibition. In their study, evaluation of platelet function before and soon after administration of the GpIIb/IIIa inhibitor showed that in the primary PCI setting SHDB(Single High Dose Bolus ) tirofiban resulted in a degree of early platelet inhibition similar to that observed with abciximab. Similarly, TIMI flow patterns and St-segment resolution—both surrogates of long-term mortality that have been consistently improved by abciximab treatment even in relatively small studies—did not differ between treatment groups(16).

In The FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) Trial tirofiban, administered as a 25 μg/kg bolus only on top of 600-mg clopidogrel and followed by a short 2-h infusion provides near-complete ADP(adenosine diphosphate) - or TRAP(thrombin receptoractivating peptide )-induced platelet inhibition for at least 6 h(17).

Marco Valgimigli et al. analysis showed that tirofiban tested at 10 μg/kg bolus regimen, which results in suboptimal platelet inhibition soon after administration, increased peri-procedural ischaemic events
mainly in terms of MI, compared with abciximab. The 25 μg/kg tirofiban bolus regimen was not associated with an increase of early ischaemic hazard when contrasted to the latter. Indeed, a trend was noted suggesting an interaction between 30-day death or MI rates (15).

**Early administration:**

Door-to-balloon time has been detected as the pivotal predictor of survival improvement (18); however, the average door-to-balloon time for patients requiring hospital transfer to primary PCI (pPCI) often exceeds 120 min, which is much longer than the 90-min target for optimal pPCI outcomes. Efforts are therefore targeted to shorten door-to-balloon times and to find the optimal medical therapy to restore blood flow to the infarcted artery during the time of STEMI diagnosis to presentation in the catheterization laboratory. The early initiation of antithrombotic treatment for STEMI patients before pPCI potentially opens the occluded vessel during transportation and reduces periprocedural thrombotic complications.

An important consideration with early anticoagulation is the accuracy in diagnosing STEMI in the ambulance.

The initial report from the On-TIME 2 (Ongoing Tirofiban In Myocardial infarction Evaluation) trial was that high-bolus dose (HBD) tirofiban, when given in the ambulance to STEMI patients who were to undergo pPCI, resulted in an improvement in ST-segment resolution, which is defined as a surrogate marker for myocardial perfusion and an indicator of improved clinical outcome (19). The trial did not, however, have sufficient power to detect the impact on mortality at 30 days. The On-TIME 2 investigators therefore designed a pre-specified pooled analysis of the placebo-controlled study phase and the open label study phase and reported that in the ambulance, early administration of HBD tirofiban for patients with STEMI results in a reduction of major adverse cardiac events (MACEs) at 30 days and a trend toward reduction in mortality at 1 year, without a clinical difference in the bleeding rate (20).

The On-TIME 2 trial shows that especially mortality and urgent PCI were reduced by early initiation of tirofiban. The reduction in mortality is probably related to the improved myocardial reperfusion. Urgent target vessel revascularization was reduced mainly through a lower rate of stent thrombosis, which again may affect mortality.

In the AGIR-2 (Comparison of the Pre-hospital or Cath-lab Administration of High Doses Tirofiban in Patients Undergoing Primary Angioplasty) study, 320 STEMI patients within 6 h of symptom onset were randomized to HBD tirofiban infusion in the ambulance or in the catheterization laboratory. All patients also received a pre-hospital loading dose of clopidogrel, aspirin, and heparin. In the pre-hospital group, tirofiban was administered 48 min earlier than in the catheterization laboratory group. However, results showed no difference in TIMI III flow at initial angiography (the primary end point). There was also no difference in ST-segment resolution or peak levels of cardiac enzymes. Although not powered for clinical events, these data actually trended toward a worse effect in the pre-hospital group (21).

The difference in clinical outcome in the On-TIME 2 trial could be explained by the time interval from
symptom onset to drug administration, which was shorter in On-TIME 2, and the fact that the control was placebo and not an active comparator as it was in similar trials.

A meta-analysis (six trials, N = 931) of patients undergoing primary PCI receiving Abciximab (three trials) or Tirofiban (three trials) reported that an early glycoprotein IIb/IIIa inhibitor administration at initial contact (emergency department or ambulance), compared with that in the cath-lab, resulted in a higher TIMI-3 flow rate (20.3 % [84/413] vs. 12.2 % [51/418]) (22). Another meta-analysis used data from 1662 patients randomly assigned to early and late glycoprotein IIb/IIIa inhibitors and showed that an early glycoprotein IIb/IIIa inhibitor administration was associated with a higher pre-procedural TIMI grade 3 flow (23).

A.A.C.M. Heestermans et al. analysis also showed that Initial patency (TIMI 3 flow) of the infarct related vessel was significantly higher in patients with upfront high dose tirofiban (HDT) therapy as compared with those who received HDT on a provisional basis. The combined incidence of 30-day death or recurrent MI occurred less often in patients with upfront HDT as compared with patients with provisional HDT use(24).

Intracoronary versus intravenous infusion during periprocedural for no reflow or slow reflow

The "no reflow phenomenon" has various definitions. Classically, it is considered to be the lack of myocardial perfusion despite opening up the epicardial vessel in the setting of primary percutaneous coronary intervention (PCI). It can occur in up to 10% of cases of primary PCI and is associated with an increased 30 day mortality if not adequately treated (32% vs. 2.8%, p<.0.001) (25). In this setting, the phenomenon is thought to be a complex process involving multiple factors that eventually lead to microvascular obstruction and endothelial disruption. Key pathogenic components include distal atherothrombotic embolization, ischemic injury, reperfusion injury, and susceptibility of coronary microcirculation to injury. Thus, pharmacologic and mechanical strategies to treat no reflow target these mechanisms.

Pharmacotherapy for the treatment of no reflow has focused primarily on two strategies: local vasodilator therapy and local antiplatelet therapy. Of these, only local vasodilator therapy has a specific guideline indication for treatment of no-reflow. The 2011 ACC PCI guidelines give a class IIa recommendation for administration of an intracoronary vasodilator (specifically, adenosine, calcium channel blocker, or nitroprusside) to treat PCI-related no reflow that occurs during primary or elective PCI.

The pharmacological mechanisms of GPI were contributed to the formation of platelet thrombi, restoration the antegrade coronary flow of occlusive vessel and reducing the incidence of the ischemia event. Tirofiban is one kind of GPI, which with high selectivity and short-acting pharmacological mechanism. During PCI, intracoronary (IC) administration of tirofiban might increase the local drug concentration and improve the coronary flow. Considering the particular mechanism, tirofiban selectively blocks the final pathway of the platelet aggregation, which might contribute to the improving TIMI flow. And the short half-life might relative to the reducing of MACE.

The therapeutic effect of intravenous administration of tirofiban on slow flow or no-reflow after
emergency PCI has not been reported, but it is found that, intravenous bolus injection of tirofiban can increase the possibility of bleeding. Intravenous administration of tirofiban can only reach plasma concentration peak after 10-30 min, with delayed time of taking effect. At the same time, due to liver metabolism, the intravenous administration reduces the drug concentration at coronary artery lesions, leading to reduced anti-platelet aggregation effect(26). Compared with intravenous administration, the direct drug injection via coronary artery can quickly achieve effective drug concentration for treatment. The drug concentrations in epicardial coronary artery and microcirculation are improved by several hundred times. So, almost all platelet membrane glycoprotein IIb/IIIa receptors in microcirculation combine with drug, but not the fibrin. The formation of white thrombus in coronary microcirculation is reduced. The higher the blocking degree of platelet membrane glycoprotein IIb/IIIa receptor is, the smaller the possibility of thrombosis in coronary microcirculation is.

H.-L. WANG et al. analysis showed that as for acute STEMI patients with heavy thrombus burden, intracoronary administration of tirofiban could markedly improve coronary blood flow and myocardial perfusion, as well as reduce the prevalence of 30-day MACE. In addition, the appearance of hemorrhagic complications was as low as it was in control group(27).

Sadegh Ali-Hassan-Sayegh et al. analysis showed that GPIIb/IIIa inhibitors injected using IC route significantly increase the chance of complete perfusion (TIMI 3 flow) compared to IV administration. IC administration of GP IIb/IIIa inhibitors, in comparison with IV route, could increase LVEF. In addition, the incidence of HF was notably lower in receivers of intracoronary antiplatelets, compared to intravenous. It can be deduced that IC administration is associated with complete perfusion, followed by increased contractility and LVEF and may prevent the progression from reversible MI to permanent HF. IC or IV administration were not significantly different regarding the incidence of re-MI. The incidence of hemorrhage was not different when administering GPIIb/IIIa inhibitors in IC or IV route(28).

CUIHUA ZHAO et al. study also showed that intra-arterial administration of tirofiban could increase the success rate of PCI (97.96 vs. 86.96%) compared with intravenous administration. Following the tirofiban injection, the platelet(PLT) dropped to 145x10^9/l in both groups, which did not meet the diagnostic criteria for thrombocytopenia, suggesting drug safety, while the PAR(platelet aggregation rate ) was lower in the coronary group than that in the intravenous group, suggesting a high level of drug absorption and an enhanced ability to inhibit platelet aggregation in the coronary group. The TIMI grade, LVEF and E/A (The ratio of the early to late ventricular filling velocities ) of the coronary group showed greater improvements than those of the intravenous group. In addition, the incidence of minor bleeding was lower in the coronary group than that in the intravenous group (29).

**ADVERSE EFFECTS AND CONTRAINDICATIONS**

The incidence of life-threatening bleeding associated with the GP IIb/IIIa antagonists has been reported to be as low as <0.2%, and appears to be lower than that of a plasminogen activator(30). A meta-
analysis by Memon et al of large trials found that the rate of intracranial hemorrhage associated with GP IIb/IIIa antagonists was not greater than that seen in control groups(31).

Thrombocytopenia is a potentially major side effect of GP IIb/IIIa antagonist administration. The mechanism of thrombocytopenia is thought to be mediated by formation of antibodies stimulated by the conformational change in the GP IIb/IIIa receptor induced by the medications(32, 33). Despite being an immune-mediated phenomenon, development of these antibodies does not appear to interfere with the efficacy of subsequent administrations of the medication, and recurrent thrombocytopenia is not observed at a higher rate than that seen upon initial exposure. In general, diminished platelet counts following GP IIb/IIIa antagonist administration is a benign complication without consequences. Rarely the thrombocytopenia may be profound and associated with hemorrhagic complications, particularly in those with low initial platelet counts and in the elderly. Treatment involves close monitoring of platelets before and after drug administration and transfusion of platelets if significant decreases are observed (34).

However, Nasir Rahman et al. reported a case of tirofiban-induced thrombocytopenia in which overall platelet count dropped precipitously to <1 × 109/L within 12 hours, followed by the patient’s relatively prolonged recovery, probably due to concomitant renal insufficiency(35).

Dimitris Sakellariou et al. reported a case of combined acute thrombocytopenia and anemia after tirofiban treatment in a patient who underwent elective percutaneous coronary angioplasty (36). Ciftci o et al. reported a case of a complication of subacute myocardial infarction, involving ventricular free wall rupture that developed after the administration of tirofiban(37).

The relative contraindications of the GPIIb/IIIa antagonists are similar to those for thrombolysis(38). Contraindications and Precautions for the tirofiban: Hypersensitivity to agent component, Active internal bleeding or recent significant G1 (gastrointestinal) or GU (genitourinary) bleed within past 6 months, History of bleeding diathesis within 30 days, Severe uncontrolled hypertension, Major surgery or trauma within previous 4 weeks, Thrombocytopenia (platelets <100,000), Stroke within previous 2 years, arteriovenous malformation, Aortic dissection and Acute pericarditis.

In CKD patients the dose should be reduced; 50% of the standard dose should be used in patients with GFR < 30 ml/min/1.73 m2. The treatment with intravenous antagonists of GP IIb/IIIa in patients with CKD is associated with a higher risk of bleeding complications, but it also significantly reduces the risk of inhospital deaths (39).

Tirofiban in combination and comparison with other medication.

In patients with ST segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (PCI), unfractionated heparin, low molecular weight heparin (LMWH), fondaparinux, and bivalirudin are all anticoagulant treatment options. The 2013 American College of Cardiology Foundation and American Heart Association guideline for management of patients with ST segment elevation myocardial infarction recommends unfractionated heparin with or without planned glycoprotein IIb/IIIa inhibitors (GpIIb/IIIa inhibitor) or bivalirudin as class I indications for patients undergoing primary PCI, with a
preference for bivalirudin over unfractionated heparin plus GpIIb/IIa inhibitor in patients at high risk of bleeding (class IIa) (40). The 2012 European Society of Cardiology guidelines, however, recommend bivalirudin over unfractionated heparin plus GpIIb/IIa inhibitor (class I) but also recommend LMWH (with or without GpIIb/IIa inhibitor) over unfractionated heparin (class IIb) (41).

In an analysis of 16 randomized trials in the era of stents and thienopyridines, unfractionated heparin plus GpIIb/IIa inhibitor were associated with a 26% reduction in the risk of myocardial infarction and 36% reduction in revascularization at the expense of a 37% increase in minor bleeding when compared with unfractionated heparin alone (42).

Bivalirudin is a direct thrombin inhibitor that works effectively on both circulating and clot-bound thrombin, with less activation of platelets and does not cause heparin induced thrombocytopenia. It has been consistently shown to reduce the risk of bleeding in randomized trials. In the HORIZONS-AMI trial, bivalirudin was associated with a significantly lower 30 day rate of major bleeding but significant increase in acute stent thrombosis compared with unfractionated heparin plus GpIIb/IIa inhibitor (43).

S Bangalore et al. analysis showed that the combination of an indirect thrombin inhibitor with a GpIIb/IIa inhibitor (unfractionated heparin plus GpIIb/IIa inhibitor and LMWH plus GpIIb/IIa inhibitor) were associated with the lowest rate of ischemic outcomes. However, there was an increase in bleeding with these agents. On the other hand, bivalirudin was associated with a significant reduction in bleeding but a significant increase in ischemic outcomes, including stent thrombosis (44).

The FABOLUS PRO Trial showed that Tirofiban, given as bolus only or bolus followed by 2-h infusion either on top of clopidogrel or prasugrel, leads to a significantly higher degree of platelet inhibition as compared with prasugrel alone. Interestingly, on top of 60-mg prasugrel, a tirofiban bolus–only regimen, irrespective of post-bolus infusion, achieves immediate and sustained near-total platelet inhibition throughout 24 h (17).

Marco Valgimigli et al. analysis showed that the use of tirofiban is an efficacious treatment option to reduce ischaemic events in patients with acute coronary syndromes and/or those undergoing PCI. When employed at high-dose bolus just prior to PCI, tirofiban may provide similar efficacy yet an improved safety profile when compared with abciximab. Overall, the safety profile seems to favour the use of tirofiban over abciximab for lower incidence of minor bleeding and thrombocytopenia, likely reflecting different chemical structures more than a difference in anti-platelet potency between these two drugs (15).

STRATEGY Investigators explained that, SHDB tirofiban resulted in a degree of early platelet inhibition similar to that observed with abciximab. Similarly, TIMI flow patterns and St-segment resolution—both surrogates of long-term mortality that have been consistently improved by abciximab treatment even in relatively small studies—did not differ between treatment groups (16).

A. Puri et al. study showed that as compared to Eptifibatide, Tirofiban results in significantly lower rates of GpIIb/IIa receptor occupancy ratio. The incidence of MACE was lower with Eptifibatide and higher dose of Tirofiban as compared to the standard dose of Tirofiban (45).
CONCLUSION

Tirofiban in general is associated with a reduction in all considered ischaemic endpoints including overall mortality, mortality or MI, and MACE rates within 30 days after treatment. Different trials shows that increasing the tirofiban bolus dose from 10 to 25 μg/kg is necessary to obtain an optimal level of platelet inhibition and in the primary PCI setting, SHDB tirofiban resulted in a degree of early platelet inhibition similar to that observed with abciximab and eptifibatide.

Multiple trials showed that early administration of HBD tirofiban for patients with STEMI results in a reduction of MACEs at 30 days and a trend toward reduction in mortality at 1 year, without a clinical difference in the bleeding rate and for no- and slow-reflow intracoronary administration is associated with complete perfusion, followed by increased contractility and LVEF and may prevent the progression from reversible MI to permanent HF. IC or IV administration were not significantly different regarding the incidence of re-MI.

The use of tirofiban may induce severe thrombocytopenia and, in some cases, a severe fall in the hematocrit level. Consequently, close monitoring of both platelet count and hematocrit early after the initiation of tirofiban infusion is mandatory and should be continued for 48 hours after the discontinuation of treatment.

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