Section A -Research paper

Rationale of Eptifibatide as a Glycoprotein IIb-IIIa Inhibitor in STEMI

Mohamed Maher Allam, Tarek Ahmed Naguib, Nader Talat Kandeel, Mohamed Helal Ahmed Helal Mohamed, Mohamed Safwat Abd El Dayem
Cardiology Department, Faculty of Medicine, Zagazig University, Egypt
Correspondence and requests for reprints to: Mohamed Helal Ahmed Helal Mohamed
E-mail: hilal49@yahoo.com , Mobile: +201067712797

Article History: Received: 21.06.2023 **Revised:**04.07.2023 **Accepted:** 16.07.2023

Abstract:

The platelet glycoprotein (GP) IIb/IIIa integrin plays a key role in mediating platelet aggregation. Blockade of the platelet GP IIb/IIIa receptor prevents arterial thrombosis in animal models much better than does aspirin. Among the most specific inhibitors in this class of drugs is eptifibatide (Integrilin^{TM}Millennium Pharmaceuticals, Inc.), a cyclic heptapeptide based on a peptide recognition sequence found in snake venom. Peptide inhibitors, such as eptifibatide, bind competitively to GP IIb/IIIa and have a short half-life, allowing the effect to be rapidly reversible and providing a favourable overall safety profile. Eptifibatide has been studied in a broad range of ischaemic coronary conditions including percutaneous coronary intervention (PCI), ST-segment and non-ST-segment acute myocardial infarction (MI) and unstable angina. In PCI and non-ST-segment MI, therapy with eptifibatide has been shown to reduce acute ischaemic complications without any increased risk of life-threatening adverse events. In the recently reported Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial, two 180 μg/kg boluses of eptifibatide, 10 min apart, followed by an 18 – 24 h infusion at 2 μg/kg/min given as adjunctive therapy in non-urgent PCI reduced the 30-day composite of death, MI and need for urgent target vessel revascularisation from 10.4 to 6.8% compared with placebo. These results were achieved under conditions of typical contemporary PCI, namely the implantation of second- and third-generation stents deployed at high balloon pressures along with modern adjunctive pharmacological treatment, particularly the universal use of thienopyridines and lower-dose heparin. Few significant pharmacological effects other than inhibition of platelet aggregation and the effect on bleeding time have been reported. Future research will focus on alternative clinical applications and combinations with other therapies to further improve cardiovascular outcomes.

Keywords: ACS, PCI, Glycoprotein IIb-IIIa Inhibitor.

DOI: 10.53555/ecb/2023.12.1148

Introduction:

Circulating platelets disclose a pivotal role in hemostasis and might become initiators of thrombotic events when endothelial injury and exposure of sub-endothelial matrix glycoprotein (GP) stimulate their adhesion, collagen and von Willebrand Factor (vWF) being the most important ligands although also surface GPs Ia/IIa, Ic/IIa, αVβ3 and Ib/IX are implicated(**1**).

However, the upmost platelet activating factor is represented by adhesion to a site of injury whereby N100 biochemical agonists come into play, including ADP, epinephrine and local mediators to quote just a few (**2**). The binding of fibrinogen and vWF and other ligands to surface GP IIb/IIIa induces a transition from a low to a high affinity state bridging platelets together and giving rise to platelet aggregation. Here is a critical point in the cascade as resting platelets have a low affinity for fibrinogen, although activated platelets can bind N40,000 molecules per cell, thus explaining the clinical importance of antiplatelet therapy and its capacity to significantly reduce the risk of serious vascular events in acute coronary syndrome (ACS) high-risk patients, including those with a prior acute ischemic event and/or ST segment elevation myocardial infarction (STEMI) (**3**).

Long-term antiplatelet agents have repeatedly been shown as key components of secondary prevention after ACS although there might be a critical balance to monitor, especially in the elderly: any effective antiplatelet regimen may be closely related to increased risk for bleeding, often necessitating discontinuation of treatment and directly impinging on a potentially worse long-term outcome (**4**).

GP IIb/IIIa inhibitors (GPI) were introduced in ACS therapy in mid 90s and competed with a wider use of ADP inhibitors and novel anticoagulant drugs until they were stepped down from class I to class II recommendation in the routine setting (**5**).

GP IIb-IIIa Inhibitors

GPIIb/IIIa inhibitors are ligand-mimetic molecules that prevent fibrinogen from binding to activated platelets, thereby directly inhibiting their aggregation. Three agents are currently in use: abciximab, a humanized antigen-binding fragment of a mouse monoclonal antibody; eptifibatide, a cyclic heptapeptide with a lysine–glycine–aspartic acid (KGD) motif mimicking the fibrinogen binding sequence within GPIIb/IIIa; and tirofiban, a nonpeptidic small molecule also mimicking the fibrinogen binding site (**6**).

First marketed in the mid-1990s, these drugs have been widely used in patients with ACS and those undergoing PCI. However, the early clinical trials assessing GPIIb/IIIa inhibitors were conducted before the routine use of P2Y 12 antagonists. Therefore, the clinical benefit derived from GPIIb/IIIa inhibitors seems to be restricted to particular high risk subgroups, such as patients with MI undergoing PCI without pretreatment with a P2Y12 antagonist (**7**).

The three approved GP IIb-IIIa inhibitors include abciximab, eptifibatide and tirofiban.

- ***Abciximab***

Abciximab is a part-murine, part-human chimeric Fab fragment of the monoclonal 7E3 IgG3 antibody against the GP IIb-IIIa receptor. Its structure was based on a murine monoclonal antibody. Abciximab is a non-competitive GP IIb-IIIa receptor inhibitor, and it is bound to platelets with very high affinity, irreversibly. It is characterized by a short plasma half-life due to its rapid binding to platelet receptor. The binding site of abciximab is located on the beta 3 chain of the GP IIb-IIIa receptor. Free plasma abciximab is cleared from the circulation within minutes, while platelet-bound drug persists for up to one week depending on the rate of platelet turnover. Therefore, being that its pharmacokinetics is not affected by kidney function, abciximab can be safely used in patients with moderate to severe renal failure, including those depending on renal dialysis, without the need for dose adjustment. The recommended dosage of abciximab is a 0.25 mg/kg intravenous bolus administered at least 10 min before the start of PCI, followed by a continuous intravenous infusion of 0.125 mcg/kg/min (to a maximum of 10 mcg/min) for 12 h (**8**).

- ***Eptifibatide***

Eptifibatide is a cyclic heptapeptide modelled on the structure of barbourin, which is a disintegrin that contains a KGD amino acid sequence that gives this molecule high specificity in binding to GP IIb-IIIa receptor. Eptifibatide acts specifically on the aIIb chain of the GP IIbIIIa receptor, which is a RGD binding site. It is a selective, competitive GP IIb-IIIa receptor inhibitor, and shows no reactivity with other integrins. It has a very rapid association and dissociation with the GP IIb-IIIa. It is cleared by the kidney, with the most of it excreted as unchanged drug in the urine. As eptifibatide was developed to be used either in patients with acute coronary syndromes (ACS) as bridging therapy to revascularization (referred to as upstream use) or directly in the catheterization laboratory immediately prior to PCI (downstream use), two distinct loading or bolus dose regimens have been investigated (180 mcg/kg intravenous (IV) bolus followed by continuous infusion of 2 mcg/kg/min for upstream use or as 180 mcg/kg IV bolus administered immediately before the initiation of PCI followed by a continuous infusion of 2 mcg/kg/min and a second 180 mcg/kg bolus 10 min after the first bolus when used in the catheterization laboratory—downstream use) (**9**).

In case of renal dysfunction (creatinine clearance < 50 ml/min), infusion should be reduced to 1 mcg/ kg/min. Eptifibatide is contraindicated in patients on dialysis (**8**).

- ***Tirofiban***

Tirofiban is a non-peptide tyrosine derivative. Similar to eptifibatide, it is an antagonist against the arginylglycylaspartic acid binding site on the aIIb chain of the GP IIb-IIIa receptor. It is also highly specific, competitive GP IIb-IIIa receptor antagonist and does not interact with other integrins. Tirofiban's affinity for the GP IIb-IIIa is

intermediate between abciximab and epitfibatide. It has also a very rapid association and dissociation with the GP IIb-IIIa and is cleared by the kidney. Tirofiban has a long plasma half-life but a short biologic half-life resulting in a rapid recovery of platelet activity, ~ 4 h following cessation of therapy (**10**).

There is about 35% unbound in the circulation with predominant renal clearance (65%) and it can be haemodialyzed. As tirofiban was developed to be used either in patients with ACS as bridging therapy to revascularization (referred to as upstream use) or directly in the catheterization laboratory immediately prior to PCI (downstream use), two distinct loading or bolus dose regimens have been investigated (0.4 mcg/kg/min infused over 30 min as upstream use or 25 mcg/kg over 3 min when used in the catheterization laboratory as downstream use), both followed by a continuous infusion. In patients with severe renal dysfunction (creatinine clearance <30 ml/min) the dosage should be reduce by 50 % (**11**).

Mechanism of action of GP IIb/IIIa inhibitors

Injury of the arterial vessel wall may be a significant determinant to initiate a thrombotic state, either as a primary mechanism which determines the incidence of ischemia and related life-threatening events (**12**) or as a consequence of mechanical stimuli involved in performing percutaneous coronary interventions (PCI): antiplatelet therapy thus became standard practice when coronary revascularization procedures were undertaken and aspirin played a pivotal role among these drugs since it inhibited cyclo-oxygenase enzymes, key factors in the platelets' activation pathways. Dual antiplatelet therapy ameliorated adverse events related to drugs used during PCI. Pre-treatment with aspirin and ticlopidine was found to be very effective to reduce acute intra-stent thrombosis. Later, a two-step strategy, separating diagnostic from interventional times was selected as dual antiplatelet therapy done before the patient was admitted to the catheterization laboratory required hours before target antiplatelet effects were obtained. By contrast, the rapid antiplatelet activity obtained by GPI opened new treatment possibilities consisting on a one-step revascularization strategy, directly downstream in the catheterization laboratory(**13**).

GP IIb/IIIa are integrins, a large family of adhesion receptors, obligate heterodimers, each one composed of a large extracellular domain, a single pass transmembrane segment and a small cytoplasmic tail (**14**). In a low affinity state GP IIb/IIIa stand on cell surface but, upon stimulations mediated by specific intracellular signals, they convert into active state, permitting linking to extracellular ligands (inside-out activation) which promotes interaction of intracellular proteins with cytoplasmic tails (outside-in activation). In the active state, the extracellular domain was shown to switch from a bent to an extended conformation(**15**).

In presence of calcium, the crystal structure of the extracellular domain is severely bent forming a compact "V" shape and in presence of magnesium integrin assumes an extended conformation: this is the "switchblade hypothesis". Cytoplasmic proteins that bind to the cytoplasmic tail play a critical role in initiating and propagating the bidirectional signaling events across the integrin. Inhibiting GP IIb/IIIa either alone or with αVβ3 receptor attenuates TF-induced prothrombin activation thus enabling both antiplatelet and anticoagulant effects. Under these perspectives GPI are able to interfere with arterial thrombosis progression mediated by the pro-coagulant activity of activated platelets. GP IIb/IIIa contains the sequence Arginin–Glycin–Aspartate. A number of antibodies against platelet GP IIb/IIIa were developed using animal models, particularly dogs. To prevent clearance of platelet with adhered antibodies, the Fc component was cleaved and, to limit immunologic response to the Fab fragments, a mouse/human chimeric antibody was developed called abciximab (**16**).

Free plasma abciximab is cleared from circulation in minutes while drug-platelet complexes persisted up to one week depending on platelet turnover. Eptifibatide and tirofiban, two small-molecules belonging to the GPI class, are respectively a peptide-mimetic linking Arginin– Glycin–Aspartate sequence with a plasma half-life of 2.5 h and a nonpeptide tyrosine derivative blocking the same site with plasma half-life of 2 h. In order to achieve sufficient therapeutic efficacy GPI need to keep N80% of GP IIb/IIIa receptor occupancy and should be administered only intravenously because, if given orally, there is a paradoxical fibrinogen binding effect related to plasmatic levels (**17**).

Thrombocytopenia and major bleeding are the most frequent complications associated with GPI. However, safety and efficacy of these agents have been widely demonstrated and it should be considered that GPI-induced thrombocytopenia is less related to increased risk of clinical complications than thrombocytopenia secondary to other causes (for example hematological, drug induced, septical or in relation to low output states) (**18**).

Rationale of GP IIb-IIIa Inhibitors in STEMI

- ***Incidence and Prognostic Implications of Reinfarction***

The prognostic impact of reinfarction after STEMI in patients treated with thrombolysis or primary angioplasty has been clearly shown in several reports. Despite improved implantation technique, coronary stenting has not reduced reinfarction compared with balloon angioplasty, ranging between 5 and 10 % in unselected patients and without the use of GP IIb-IIIa inhibitors (**8**).

- ***Incidence and Prognostic Implications of Distal Embolisation***

Despite successful mechanical recanalization of the infarct related artery, suboptimal myocardial reperfusion may be observed, resulting in unfavorable outcome. In the last years, growing interest has been

focused on the role of distal embolization as major determinant of poor reperfusion (**19**).

It was demonstrated that plaque composition (large amounts of necrotic core as evaluated by Virtual Histology IVUS) may certainly influence the occurrence of distal embolization as much as thrombus composition (**20**).

However, it must be recognized that the thrombotic burden may be extremely variable among patients. The identification of those patients at higher risk for distal embolization would be crucial, especially when the decision to administer adjunctive antithrombotic therapy is undertaken after diagnostic angiography. In an analysis by the Zwolle group, poor myocardial perfusion was more often observed in small vessels despite less distal embolization, compared with larger vessels (**21**).

Yunoki and his colleagues found that large vessel size, together with hyperglycemia, balloon pre dilatation and thrombus composition were independent predictors of distal embolization (**20**). It was confirmed that patients with advanced Killip class at presentation, diabetic patients and the elderly are at higher risk for this complication, while no impact has been observed by gender or hypertension. Finally, whereas intuitively the negative prognostic impact of distal embolization is expected to be influenced by ischemia time, the data on this issue are still contrasting (**22**).

- ***No-Reflow Phenomenon***

In addition to distal embolization and mechanical compression, considerable interest has been focused in the last decades on inflammation and spasm of the microcirculation as major determinants of no-reflow phenomenon. Soon after infarct-related artery (IRA) recanalization, neutrophil activation and accumulation in the damaged myocardium has been demonstrated (**23**).

- ***Ischemia Time and Early Reperfusion***

Primary angioplasty is able to restore TIMI 3 flow independently from the time of treatment; this cannot abrogate the deleterious effects of ischemia time on myocardial necrosis and perfusion. The impact of ischemia time on infarct size has been demonstrated in several studies using nuclear techniques or cardiac magnetic resonance imaging (MRI), definitively supporting the clear impact of ischemia time on infarct size and outcome even in patients undergoing mechanical reperfusion (**24**).

Timing of GPI administration

Current European Society of Cardiology guidelines on ACS patients without ST segment elevation myocardial infarction (NSTEMI) no longer consider routinely upstream use of GPI. At present they restricted its use in active ongoing ischemia among high risk patients or when double antiplatelet therapy is unfeasible and PCI are mentioned only by the following statements: “GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications, Class (IIa); It is not recommended to administer GPIIb/IIIa inhibitors in patients in whom coronary anatomy is not known, Class (III)”. However, it is reasonable to use GPI in patients undergoing PCI based on

angiographic results such as presence of a thrombus or troponin elevation, previous treatment with P2Y12 inhibitors, patient age and bleeding risk. It is also reasonable to combine GPI with dual antiplatelet therapy in patients undergoing high risk PCI and without high bleeding risk. In association with novel anticoagulant drugs such as bivalirudin, GPI are not recommended because of worse outcome (**5**).

In STEMI, the above mentioned guidelines, declare that the role of GPI during primary PCI and the era of novel antiplatelet drugs, particularly prasugrel and ticagrelor, is not well defined. It is reasonable to use them in STEMI, similar to NSTEMI, as bailout therapy when there is angiographic evidence of a large thrombus, slow-flow or no reflow or other particular cases. However, GPI are not recommended when bivalirudin is used (**25**).

As a consequence, in STEMI patients, periprocedural antithrombotic medication in primary PCI stepped down GPI from I to II class of recommendation, whose level of evidence was judged A for abciximab and B for high double bolus dose eptifibatide or high bolus dose tirofiban. Intra-venous route should remain the standard strategy, although intra-coronary administration may be considered (**26**).

Alternative protocols of GPI administration

- ***Bolus only and abbreviated infusion***

The recommendation of long duration infusion of GPI (12–24 h) was based on trial data predating the era of stents and dual antiplatelet. As thienopyridine loading is expected to achieve adequate antiplatelet activity within 30 min to few hours particularly with the newer and potent antiplatelet, it may be reasonable to limit the use GP IIb-IIIa inhibitor in the bolus only or bolus and short duration infusion **(27).**

- ***Intracoronary injection of bolus doses***

Intracoronary injection (IC) of GPI resulted in higher receptor occupancy rates and better thrombus resolution in experimental models. Improved epicardial and myocardial perfusion were found and were also associated with less adverse events. In the major AIDA-STEMI trial, 2065 STEMI patents undergoing PCI were randomly assigned to receive abciximab by an IV infusion or directly into the infarct related coronary artery through guiding catheter. The primary composite outcome of death, new MI, new heart failure at 90 days, was not different between two groups. However, the IC administration was associated with reduced incidence of heart failure (**28**).

In the MRI sub study; there was no significant difference in the infarct size between the groups (**29**). In the INFUSE AMI study, the selective infusion of IC abciximab through a specialized perfusion catheter was associated with statistically significant 2% reduction in the infarct size by MRI (**30**). Further, in a registry of 104 patients evaluated by intracoronary administration of GPI bolus doses was associated with reduction of thrombus burden and improved flow following PCI (**31**). A study by **Sengottuvelu and Ravi**

Sekar (32) also has shown similar outcomes in STEMI patients undergoing primary PCI.

Platelet GP IIb/IIIa inhibition in ACS during PCI

The goals of any reperfusion strategy in ACS are fast restoration of both epicardial blood flow and myocardial microcirculation. One possible mechanism by which GP IIb/IIIa antagonists exert their beneficial effects is by reducing platelet aggregation and micro-embolization downstream during mechanical reperfusion and thereby preserving the microcirculation. The role of periprocedural GP IIb/IIIa inhibition in the setting of PCI was established by several randomized, placebo-controlled trials enrolling over 30,000 patients. As adjunctive therapy for PCI, the primary objective of the randomized trials with intravenous GP IIb/IIIa inhibitors was to reduce a 30-day ischemic composite end point, namely, death, myocardial infarction (MI) and urgent revascularization. The most compelling support for platelet GP IIb/IIIa inhibition therapy comes from the abciximab trials. They have demonstrated a clinically important reduction in early ischemic events, sustained beneficial effects at long-term follow-up, and benefits that extends similarly to all interventional devices, lesion complexities and patient acuities (**33**).

In the era of balloon angioplasty, the addition of GPIIb/IIIa inhibitors to the armamentarium of antiplatelet agents represented a significant therapeutic advance compared with therapy with aspirin plus unfractionated heparin. GPIIb/IIIa inhibitors inhibit the final pathway of platelet aggregation by competing with von Willebrand factor and fibrinogen for GPIIb/IIIa receptor binding. GPIIb/IIIa inhibitors provide fast and potent antiplatelet effects. Compared with cangrelor, these agents inhibit the platelet response to all agonists and are therefore more potent antiplatelet agents than cangrelor. GPIIb/IIIa inhibitors provide rapid and nearly complete platelet aggregation inhibition, overcoming the delayed and poor platelet inhibition induced by a clopidogrel loading dose. The benefits of pretreatment with GPIIb/IIIa inhibitors were noted in high-risk patients in early clinical trials that showed a significant reduction in MI and urgent revascularization before and after angioplasty. GPIIb/IIIa inhibitor therapy has been associated with a reduction in adverse cardiovascular events, including MI, at the expense of increased bleeding and thrombocytopenia (**34**).

Contradicting evidence was shown in the benefit of routine use of GPIIb/IIIa inhibitors. In a meta-analysis of 10,123 patients undergoing primary PCI, nonfatal MI at 30 days was reduced from 8.3 to 5.1% with use of GPIIb/IIIa inhibitors at the expense of a significant increase in the risk of minor bleeding and thrombocytopenia. The increase in major bleeding events was not significant. The reduction in nonfatal MI was irrespective of thienopyridine pre-treatment, and upon meta-regression, the benefits of GPIIb/IIIa inhibitors were consistent in earlier versus more recent clinical trials. There were no differences in 30-day or 1-year mortality rates. With the

introduction of more potent adenosine diphosphate-receptor blockers, the incremental value of GPIIb/IIIa inhibitors in reducing periprocedural MI remains to be determined. Currently, the administration of GPIIb/IIIa inhibitors is an accepted treatment option for patients undergoing primary PCI and patients with visible thrombus burden (**35**).

Another approach in administering GPIIb/IIIa inhibitors is through the intracoronary route of delivery. This approach can lead to a higher local concentration of antiplatelet agent aiding in higher receptor occupancy with disruption of platelet crosslinking and augmenting thrombus resolution to a greater extent (**36**). Intracoronary GPIIb/IIIa inhibitor therapy may also limit the risk of myocardial damage from thromboembolism in the microvasculature. Intracoronary administration of GPIIb/IIIa inhibitor has been tested in several small studies and shown to be safe and associated with some benefits when compared with intravenous administration, but these results have not been confirmed in large-scale clinical trials(**37**).

Strategies employing shorter GPIIb/IIIa inhibitor infusions and use of a transradial approach may provide greater degrees of net benefit. Earlier trials of GPIIb/IIIa inhibitors employed 18-24 hour infusions, and these durations of therapy were associated with greater bleeding than their comparator arms that included use of bivalirudin (**38**).

GPIIb/IIIa inhibitors have the greatest role in the treatment of high-risk patients and those with high-risk PCI angiographic features (visible thrombus and high-risk anatomy) who have low risk of bleeding.[48] Currently, the American College of Cardiology and American Heart Association guidelines provide a Class IIa recommendation for GPIIb/IIIa inhibitors at the time of primary PCI (abciximab, double-bolus eptifibatide, or high-bolus-dose tirofiban) in selected patients with STEMI receiving unfractionated heparin (with or without stenting or clopidogrel pretreatment), and a Class IIb indication for intracoronary Abciximab (**39**).

The ideal parenteral antiplatelet agent would provide immediate and robust periprocedural ischemic benefit without attendant excess bleeding risk. GPIIb/IIIa inhibitors have been associated with reduced thrombotic events after PCI compared with heparin and bivalirudin therapy alone, but their routine use, notably with prolonged infusion durations, has been associated with increased severe bleeding complications and potentially increased PCI-related costs (**40**). Provisional use of GPIIb/IIIa inhibitors, shortened GPIIb/IIIa inhibitor infusion duration, novel delivery systems, and augmented use of radial access will likely improve the net clinical benefit of GPIIb/IIIa inhibitors. Moreover, the effect of inhibition of all agonist-induced pathways of platelet aggregation by GPIIb/IIIa inhibitors compared with cangrelor may provide greater protection from ischemic events. Furthermore, recent advances in the overall

quality in periprocedural care that have led to stepwise improvements in PCI outcomes will potentially influence the risk-benefit profile of GPIIb/IIIa inhibitors. At present, there are no randomized clinical trials comparing the utility of cangrelor and GPIIb/IIIa inhibitors. GPIIb/IIIa inhibitor use is expected to continue in bailout/rescue scenarios, but the introduction and uptake of cangrelor may also limit their use in clinical practice (**41**).

References:

1. Ting HJ and Khasawneh FT (2010). Platelet function and Isoprostane biology. Should isoprostanes be the newest member of the orphan-ligand family? J Biomed Sci. 2010 Apr 6; 17(1):24.
2. Kristensen SD, Würtz M, Grove EL, et al (2012). Contemporary use of glycoprotein IIb/IIIa inhibitors. Thromb Haemost. 2012 Feb; 107(2):215-24.
3. Valgimigli M and Tebaldi M (2010). Safety evaluation of tirofiban. Expert Opin Drug Saf. 2010 Sep; 9(5):801-19.
4. Puddu PE, Schiariti M and Bugiardini R (2011). Glycoproteins IIb/IIIa antagonists in acute coronary syndromes undergoing PCI: a long way to select optimal agent and route. ISRN Vasc Med. 2011; 1:1–9.
5. Roffi M, Patrono C, Collet JP, et al (2016); ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016 Jan 14; 37(3):267-315.
6. Michelson AD (2010). Antiplatelet therapies for the treatment of cardiovascular disease. Nat Rev Drug Discov. 2010; 9:154–169.
7. Bosch X, Marrugat J and Sanchis J (2013). Platelet glycoprotein IIb/IIIa blockers during percutaneous coronary intervention and as the initial medical treatment of non-ST segment elevation acute coronary syndromes. Cochrane Database Syst Rev. 2013 Oct 18 ;(10):CD002130.
8. De Luca G, Savonitto S, van't Hof AW, et al (2015). Platelet GP IIb-IIIa Receptor Antagonists in Primary Angioplasty: Back to the Future. Drugs, 75(11), 1229–1253.
9. Zeymer U, Margenet A, Haude M, et al (2010). Randomized Comparison of Eptifibatide Versus Abciximab in Primary Percutaneous Coronary Intervention in Patients With Acute ST-Segment Elevation Myocardial Infarction. J Am Coll Cardiol. 2010; 56(6):463-9.
10. Schneider DJ, Herrmann HC, Lakkis N, et al (2003). Increased concentrations of tirofiban in blood and their correlation with inhibition of platelet aggregation after greater bolus doses of tirofiban. Am J Cardiol. 2003 Feb 1; 91(3):334-6.

11. Danzi GB, Sesana M, Capuano C, et al (2004). Comparison in patients having primary coronary angioplasty of abciximab versus tirofiban on recovery of left ventricular function. Am J Cardiol. 2004 Jul 1;94(1):35-9.
12. Puddu P.E and Menotti A (2015). Natural history of coronary heart disease and heart disease of uncertain etiology: findings from a 50-year population study. Int. J. Cardiol. 2015; 197: 260-264
13. Gulec S, Ozdol C, Vurgun K, et al (2008). The effect of high-dose aspirin pre-treatment on the incidence of myonecrosis following elective coronary stenting. Atherosclerosis. 2008; 197(1):171–176.
14. Yang XZ (2009). Pharmacological effect of natural glycoproteins. World J. Integr. Tradit. West Med. 4: 375– 376.
15. Kurtz L, Kao L, Newman D, et al (2012). Integrin αIIbβ3 inside-out activation: an in situ conformational analysis reveals a new mechanism. J Biol Chem. 2012 Jun 29; 287(27):23255-65.
16. Schneider DJ (2011). Anti-platelet therapy: glycoprotein IIb-IIIa antagonists. Br J Clin Pharmacol. 2011 Oct; 72(4):672-82.
17. Armstrong PC and Peter K (2012). GPIIb/IIIa inhibitors: from bench to bedside and back to bench again. Thromb Haemost. 2012 May; 107(5):808-14.
18. Schiariti M, Saladini P, Cuturello D, et al (2014). Decline in platelet count and long-term post-PCI ischemic events: implication of the intra-aortic balloon pump. Vasc. Pharmacol. 2014; 60: 25-31.
19. De Luca G, Smit JJ, Ernst N, et al (2005). Impact of adjunctive tirofiban administration on myocardial perfusion and mortality in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction. Thromb Haemost. 2005 May; 93(5):820-3.
20. Yunoki K, Naruko T, Sugioka K, et al (2013). Thrombus aspiration therapy and coronary thrombus components in patients with acute ST-elevation myocardial infarction. J Atheroscler Thromb. 2013; 20(6):524-37.
21. De Luca G, Navarese E and Marino P (2009). Risk profile and benefits from GPIIb–IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. Eur. Heart J; 30(22):2705–13.
22. De Luca G, Wirianta J, Lee JH, et al (2014) Sirolimus-eluting versus paclitaxel-eluting stent in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. Thromb Thrombolysis. 2014 Oct; 38(3):355-63.
23. Niccoli G, Rigattieri S, De Vita MR, et al (2013). Open-label, randomized, placebo-controlled evaluation of intracoronary adenosine or nitroprusside after thrombus aspiration during

primary percutaneous coronary intervention for the prevention of microvascular obstruction in acute myocardial infarction: the REOPEN-AMI study (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction). JACC Cardiovasc Interv. 2013 Jun; 6(6):580-9.

24. Guerchicoff A, Brener SJ, Maehara A, et al (2014). Impact of delay to reperfusion on reperfusion success, infarct size, and clinical outcomes in patients with ST-segment elevation myocardial infarction: the INFUSE-AMI Trial (INFUSE-Anterior Myocardial Infarction). JACC Cardiovasc Interv. 2014 Jul;7(7):733-40.
25. Iannetta L, Puddu PE, Cuturello D, et al (2013). Is There Still a Role for Glycoprotein IIb/IIIa Antagonists in Acute Coronary Syndromes? Cardiol Res. 2013 Feb; 4(1):1-7.
26. Steg PG, James SK, Atar D, et al (2012). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012; 33(20):2569–2619.
27. Subban V and Chandra SK. Glycoprotein IIb-IIIa inhibitors - do we still need them? Indian Heart J. 2013 May-Jun; 65(3):260-3.
28. Thiele H, Zeymer U, Neumann FJ, et al (2012); IABP-SHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012 Oct 4; 367(14):1287-96.
29. Eitel I, Desch S, Thiele H, et al (2013). Reply. J Am Coll Cardiol. 2013 Jul, 62 (5) 481–482.
30. Stone GW, Maehara A, Witzenbichler B, et al (2012). INFUSE-AMI Investigators. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. JAMA. 2012 May 2; 307(17):1817-26.
31. Maluenda G, Sizemore BC, Revtyak G, et al (2013). Clearway Registry Investigators. Intracoronary glycoprotein IIb/IIIa inhibitor infusion via a perfusion coronary catheter to decrease thrombus burden: results from the ClearWay™ Multicenter Registry. Cardiovasc Revasc Med. 2013 Sep-Oct; 14(5):280-3.
32. Sengottuvelu G and Ravi Sekar V (2013). Intracoronary abciximab in STEMI using local drug delivery catheter - single center experience. Indian Heart J. 2013 May-Jun; 65(3): 256-9.
33. Centurión OA (2016) Current Role of Platelet Glycoprotein IIb/IIIa Inhibition in the Therapeutic Management of Acute Coronary Syndromes in the Stent Era. J Cardiol Curr Res 5(5): 00175.
34. Safley DM, Venkitachalam L, Kennedy KF, et al (2015). Impact of glycoprotein IIb/IIIa inhibition in contemporary percutaneous coronary intervention for acute coronary syndromes: insights

from the national cardiovascular data registry. JACC Cardiovasc Interv; 2015 Oct; 8(12):1574-82.

35. Winchester DE, Wen X, Brearley WD, et al (2011). Efficacy and safety of glycoprotein IIb/IIIa inhibitors during elective coronary revascularization: a meta-analysis of randomized trials performed in the era of stents and thienopyridines. J Am Coll Cardiol. 2011 Mar 8; 57(10):1190-9.
36. Wilmer CI (2018): Intracoronary high-dose bolus tirofiban administration during complex coronary interventions: A United States-based case series. Cardiovascular Revascularization Medicine, 2018 Jan-Feb; 19(1 Pt B):112-116.
37. Mostafa S, Nab MH, Elrabat K, et al (2017). Comparison between bolus intracoronary versus bolus intravenous injection regimens of eptifibatide during primary PCI in patients with anterior STEMI. Atheroscler Suppl 2017; 25:e3.
38. Ahsan SA, Haque KS, Arzu J, et al (2017). Immediate & Short Term Outcome of Using Single Bolus Eptifibatide in Percutaneous Coronary Intervention: A Randomized Control Study. Mymensingh Med J 2017; 26:300-5.
39. Amsterdam EA, Wenger NK, Brindis RG, et al. (2014) AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 64:e139-e228.
40. O'Gara PT, Kushner FG, Ascheim DD, et al (2013). 2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation, 2013; 127: e362-e425.
41. Curzen N, Gurbel PA, Myat A, et al (2013). What is the optimum adjunctive reperfusion strategy for primary percutaneous coronary intervention? Lancet 2013; 382:633-43.