

## The Evidence for Downgrading the Use of Glycoprotein IIb/IIIa Inhibitors in Patients with Non ST Elevation Myocardial Infarction

Shabnam Rashid<sup>1\*</sup>, Sandra Elsheikh<sup>1</sup> and Chris Sawh<sup>2</sup>

<sup>1</sup>Leeds General Infirmary, Great George Street, Leeds, West Yorkshire, LS1 3EX, UK

<sup>2</sup>Northern General Hospital, Herries Road, Sheffield, South Yorkshire, S5 7AU, UK

\*Corresponding author: Dr. Shabnam Rashid, BSc, MBChB, Leeds General Infirmary, Great George Street, Leeds, West Yorkshire, LS1 3EX, UK, Tel: 01132432799; E-mail: [shabnamrashid@doctors.org.uk](mailto:shabnamrashid@doctors.org.uk)

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### Introduction

The use of glycoprotein IIb/IIIa receptor inhibitors in patients with non ST elevation myocardial infarction and unstable angina has reduced considerably since the introduction of potent antiplatelets. The glycoprotein IIb/IIIa receptor inhibitors were introduced before the P2Y<sub>12</sub> receptor inhibitors and thus majority of the trials were done without the P2Y<sub>12</sub> receptor inhibitors. This article will explore the changes in the European Society of Cardiology guidelines on the use of glycoprotein IIb/IIIa receptor inhibitors in patients with non ST elevation myocardial infarction. Of importance, there are limited studies examining the role of glycoprotein IIb/IIIa receptor inhibitors with dual antiplatelet therapies and subgroup analysis from trials have been used to develop the guidelines.

**Keywords:** Antiplatelet therapies; Acute coronary syndrome; Percutaneous coronary intervention.

### Discussion

Platelets play a key role in vascular occlusion during an acute coronary syndrome (ACS) as platelet aggregation occurs. The glycoprotein (GP) IIb/IIIa receptor on the platelet surface becomes activated during an acute coronary event and binds fibrinogen. Fibrinogen results in platelet aggregation by binding onto the GPIIb/IIIa receptor on adjacent platelets [1].

There are currently three intravenous GPIIb/IIIa receptor inhibitors used in clinical practice; tirofiban, eptifibatide and abciximab.

Tirofiban is a non peptide GPIIb/IIIa receptor inhibitor with a half life of 2 hours [1]. Eptifibatide is a cyclic peptide [2] and abciximab is a monoclonal antibody fragment [3].

Eptifibatide and tirofiban have shorter half lives in comparison to Abciximab. Therefore in high risk patients who require coronary artery bypass surgery, eptifibatide and tirofiban can be discontinued 2-4 hours prior to surgery. Abciximab needs to be discontinued 12 hours prior to coronary artery bypass graft surgery [3].

Clinical trials with GPIIb/IIIa receptor inhibitors in patients with non ST elevation myocardial infarction (NSTEMI) have demonstrated significant benefit with a reduction in mortality and reinfarction rates [4-6]. The majority of trials with GPIIb/IIIa receptor inhibitors were done prior to the use of dual antiplatelet therapy (DAPT) for ACS.

Patients with ACS were routinely treated with aspirin, heparin and GPIIb/IIIa receptor inhibitors due to evidence which suggested benefit [4-6].

### European society of cardiology 2002 on the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.

The use of GPIIb/IIIa receptor inhibitors is recommended as a class I indication in all patients who are troponin positive and treated with aspirin and heparin [7].

In the PERSUIT trial, eptifibatide with aspirin and heparin was compared to placebo therapy in patients with a diagnosis of ACS. There was a 1.5% absolute reduction in the incidence of primary end point of death and non-fatal myocardial infarction (MI) in the eptifibatide group at 96 hours. This benefit was apparent up to 30 days. Gender differences were prominent with males having better outcomes although reasons for this were unclear. Patients who underwent percutaneous coronary intervention (PCI) within 72 hours of the study had a significant reduction in death and non-fatal MI (11.6% with eptifibatide and 16.7% with placebo). Bleeding was more prevalent in patients who received eptifibatide although there was no significant increase in hemorrhagic stroke [4].

The PRISM PLUS study examined the combination of tirofiban and heparin versus heparin alone in patients with NSTEMI. Patients in both groups received aspirin. The combination therapy with tirofiban and heparin was superior to heparin alone at 7 days, 30 days and 6 months. The composite end point of death or MI was 12.9% in the combined group versus 17.9% in the heparin group. Benefit was seen in patients treated medically or by PCI. Bleeding rates were higher in patients who received combination therapy [5].

In the PRISM study the use of aspirin with 48 hour infusion with tirofiban or 48 hour infusion with heparin was assessed. The composite endpoint of death, MI, refractory ischemia after 48 hours of treatment was 32% lower in patients who received tirofiban. The composite end point at 30 days was similar for both groups but appeared to favour the use of aspirin with tirofiban. Major bleeding rates were similar in both groups [6].

Although several trials have demonstrated positive outcomes with abciximab the GUSTO IV trial failed to reduce rates of death/MI at 30 days with abciximab. In this trial the effects of abciximab in 7800 patients with NSTEMI not undergoing early revascularisation was assessed. Patients were assigned to a placebo group, abciximab bolus with 24 hour infusion, or abciximab bolus followed by 48 hour infusion. There was an increase in the rate of events; 8.0% in the placebo, 8.2% in the 24 hour and 9.1% in the 48 hour treated groups. The explanations for the results were unclear and given that this was a large trial the results were unlikely to be due to chance. Therefore in patients who were treated medically abciximab was not beneficial [8].

In a meta-analysis of the trials involving 29570 patients with NSTEMI and unstable angina there was a reduction in death/MI at 30 days with the use of GPIIb/IIIa receptor inhibitors from 11.5% to 10.7% in patients with ACS. The benefit was more pronounced in patients who received GPIIb/IIIa receptor inhibitors during PCI. In this group death and MI reduced from 13.6% to 10.5%. There did not appear to be any benefit when GPIIb/IIIa receptor inhibitors were discontinued before PCI. In patients who were treated medically there was no mortality benefit or reduction in recurrent MI with GPIIb/IIIa receptor inhibitor use. The use of GP IIb/IIIa receptor inhibitors was associated with an increase in major bleeding complications, but intracranial bleeding was not significantly increased [9].

### **European society of cardiology NSTEMI 2007 guidelines**

In the ESC 2007 NSTEMI guidelines there was no longer a class I indication to use GPIIb/IIIa receptor inhibitors in all NSTEMI patients. There was a class I indication in high-risk patients proceeding to PCI following angiography.

GPIIb/IIIa receptor inhibitors were also recommended as a class IIa indication in patients with intermediate to high risk features such as raised troponin, diabetes mellitus or ST depression [10].

After the introduction of P2Y12 inhibitors most notably Clopidogrel in 2001, further trials with GPIIb/IIIa receptor inhibitors were performed to determine the optimal timing of administering GPIIb/IIIa receptor inhibitors.

The ACUTY TIMINING and EARLY ACS trials have shown that there is no benefit in the use of GP IIb/IIIa receptor inhibitors pre-PCI [11-12].

In the ACUTY timing trial 9207 patients were randomised to GP IIb/IIIa receptor inhibitor pre PCI or during PCI. GP IIb/IIIa receptor inhibitors were used for 18.3 hours in the pre-PCI group and 13.1 hours in the deferred group. In this trial 64% of patients received a P2Y12 receptor inhibitor before angiography or PCI. There was no significant difference in ischaemic events between both groups, however 30 day non-coronary artery bypass graft surgery related bleeding rates were significantly higher in patients who received GP IIb/IIIa receptor inhibitors pre-PCI; 6.1% versus 4.9% in the deferred group. Therefore there is no benefit in administering GP IIb/IIIa receptor inhibitors pre-PCI [11].

In the EARLY ACS trial 9429 patients with NSTEMI assigned to an invasive strategy were randomized to receive eptifibatide pre PCI for 12 hours, or eptifibatide after angiography for PCI. Pre-procedure clopidogrel was given to 75% of patients. At 96 hours there was no significant reduction in the composite primary end point of death, MI, recurrent ischemia requiring urgent revascularization, or the occurrence of thrombotic complication during PCI requiring bolus eptifibatide (9.3% if eptifibatide was given pre-PCI versus 10% if given after angiography). The secondary endpoint of death from any cause or MI at 30 days was also similar; 11.2% if eptifibatide was given pre-PCI and 12.3% if given after angiography. Major bleeding rates were higher among patients who received eptifibatide pre-PCI compared to those who received eptifibatide after angiography; 2.6% versus 1.8%. The use of eptifibatide prior to angiography was not superior to the use of eptifibatide after angiography and was associated with excess bleeding rates. In patients who were managed medically there was no benefit in

administering eptifibatide when compared to placebo and was associated with excess bleeding [12].

These trials therefore demonstrated that there was no benefit in administering GP IIb/IIIa receptor inhibitors in patients with NSTEMI prior to angiography and was associated with excess rates of bleeding [11,12].

### **European society of cardiology NSTEMI 2011 guidelines**

In the ESC 2011 NSTEMI guidelines the use of GP IIb/IIIa receptor inhibitors in patients treated with DAPT is recommended as a class I indication in patients undergoing high-risk PCI (elevated troponin, visible thrombus) if the risk of bleeding is low.

In patients treated with DAPT with intermediate to high risk features such as raised troponin, diabetes mellitus or ST depression the use of GPIIb/IIIa inhibitors was a class IIb recommendation. Furthermore GP IIb/IIIa receptor inhibitors are not recommended routinely before angiography or those being treated conservatively (class IIIa indication) [13]

### **European society of cardiology NSTEMI 2015 guidelines**

The most recent ESC NSTEMI 2015 guidelines no longer recommend the use of GP IIb/IIIa receptor inhibitors as a class I indication. GP IIb/IIIa inhibitors should be considered for bailout situations or thrombotic complications during PCI (class IIa). In patients in whom the coronary anatomy is unknown then GP IIb/IIIa receptor inhibitors should not be used (class IIIa) [14].

The trials have consistently shown higher rates of bleeding with pre-PCI GP IIb/IIIa receptor inhibitor use [4-6,9,11,12]. There was no mortality or MI benefit in patients who received GP IIb/IIIa receptor inhibitors pre-PCI [11,12]. This may account for the class III indication for the use of GP IIb/IIIa receptor inhibitors if coronary anatomy is unknown. Therefore GP IIb/IIIa receptor inhibitors should be withheld until the patients coronary anatomy is known [14].

There is a lack of trials assessing the effects of GP IIb/IIIa receptor inhibitors with aspirin and P2Y12 inhibitor in the setting of NSTEMI patients. In the ISAR-REACT-2 trial, 2022 high risk NSTEMI patients undergoing PCI were randomized to either abciximab or placebo following pre-treatment with aspirin and 600 mg of clopidogrel. The 30 day composite endpoint of death, MI, or urgent target vessel revascularization was significantly less in the abciximab group; 8.9% vs. 11.9% placebo. The effect was prevalent in high risk groups such as troponin-positive patients receiving abciximab; 13.1% vs. 18.3% placebo. There was no benefit with abciximab in troponin-negative patients or diabetic patients. The low number of diabetic patients in this trial may have been too low to detect any statistical benefit [15].

Subgroup analysis of the PLATO and TRITON trial also provides further evidence regarding the use of GP IIb/IIIa receptor inhibitors in ACS patients treated with DAPT [16,17].

The TRITON trial demonstrated the superiority of prasugrel over clopidogrel in patients with ACS since there was a reduction in death from cardiovascular causes, non fatal MI and stroke. In this trial GP IIb/IIIa receptor inhibitors were used in 55% of patients. Prasugrel reduced rates of death, MI, or stroke compared to clopidogrel both with (6.5% prasugrel vs. 8.5% clopidogrel) and without (4.8% prasugrel

vs. 6.1% clopidogrel) GP IIb/IIIa receptor inhibitors. Patients that received GP IIb/IIIa receptor inhibitor had higher rates of TIMI major and minor non-coronary artery bypass graft surgery bleeding, although this was not affected by the type of antiplatelet used [16].

In the PLATO trial patients with ACS were found to have lower death rates from vascular causes, MI or stroke with ticagrelor when compared to clopidogrel. GP IIb/IIIa receptor inhibitors were used in 27% of these patients. In the PLATO trial, the rates of death, MI, or stroke in patients receiving GP IIb/IIIa receptor inhibitor was 10.0% ticagrelor vs. 11.1% clopidogrel. In those not receiving a GP IIb/IIIa receptor inhibitor the primary end point was achieved in 9.7% ticagrelor vs. 11.9% clopidogrel.

The use of GpIIb/IIIa inhibitors did not alter the effectiveness of ticagrelor compared to clopidogrel at 30 days and 12 months [17].

In view of these trials, GP IIb/IIIa receptor inhibitor can be combined with aspirin and a P2Y12 inhibitor for patients with NSTEMI undergoing PCI with a high risk of procedural MI and without high bleeding risk [14].

### Side effects of GP IIb/IIIa receptor inhibitors

The trials have consistently shown higher rates of bleeding with GP IIb/IIIa receptor inhibitor use. Therefore whenever GP IIb/IIIa

receptor inhibitor are required the risk of bleeding versus ischemic events needs to be carefully addressed. One of the common side effects with GP IIb/IIIa inhibitors is thrombocytopenia. Acute thrombocytopenia occurs at rates ranging from 0.5% to 5.6% in clinical trials with GP IIb/IIIa receptor inhibitors. Delayed thrombocytopenia may also occur after 5–11 days and tends to be reversible [14]. Abciximab more than doubles the incidence of severe thrombocytopenia in comparison to other GP IIb/IIIa receptor inhibitors. In the TARGET study, the efficacy of abciximab was compared to tirofiban in NSTEMI patients undergoing PCI.

Thrombocytopenia developed in 2.4% of the patients treated with abciximab and in 0.5% of those treated with tirofiban. Abciximab was superior to tirofiban since there was a reduction in the risk of death, MI, and urgent revascularization at 30 days, but the difference was not significant at 6 months. In this study tirofiban was given as a bolus dose of 10 µg per kilogram of body weight, followed by an infusion of 0.15 µg/kilogram per minute (Table 1).

Further studies have shown that high dose bolus tirofiban (25 µg/kg followed by infusion) has similar efficacy to abciximab. There are no comparable data for eptifibatide [18].

ESC guideline	Recommendation	Class
2002	GPIIb/IIIa receptor inhibitors indicated in all patients who are troponin positive and treated with aspirin and heparin	I
2007	GPIIb/IIIa receptor inhibitors indicated In high-risk patients proceeding to PCI following angiography. In patients treated with DAPT, GPIIb/IIIa receptor inhibitors should be considered In patients with intermediate to high risk features such as raised troponin, diabetes mellitus or ST depression.	I IIa
2011	In patients treated with DAPT, GPIIb/IIIa receptor inhibitors recommended in patients undergoing high-risk PCI (elevated troponin, visible thrombus) if the risk of bleeding is low. In patients treated with DAPT with intermediate to high risk features such as raised troponin, diabetes mellitus or ST depression the use of GPIIb/IIIa inhibitors maybe considered. GP IIb/IIIa receptor inhibitors are not recommended routinely before angiography in an invasive treatment strategy or those treated medically.	I IIb IIIa
2015	GP IIb/IIIa inhibitors should be considered for bailout situations or thrombotic complications during PCI. GP IIb/IIIa receptor inhibitors should not be used in patients in who the coronary anatomy is unknown.	IIa IIIa

**Table 1:** Summary of the ESC guidelines for the use of GPIIb/IIIa receptor inhibitors in patients with NSTEMI [4-6,9,11,12,15,16,17].

### Conclusion

The introduction of potent P2Y12 receptor inhibitors has resulted in a significant decline in the use of glycoprotein IIb/IIIa receptor inhibitors over the past decade in patients with non ST elevation myocardial infarction. There is no longer a class I indication for the use of glycoprotein IIb/IIIa receptor inhibitors in non ST elevation myocardial infarction patients. It can be considered during percutaneous coronary intervention for high risk cases. When there is a clinical need for glycoprotein IIb/IIIa receptor inhibitors the risk of bleeding versus ischemia needs to be assessed.

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