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Platelet Glycoprotein IIb/IIIa Receptor Antagonists in Non-ST Segment Elevation Acute Coronary Syndromes

A Review and Guide to Patient Selection

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Abstract

Platelet glycoprotein (Gp) IIb/IIIa receptor antagonists improve outcomes in patients with acute coronary syndromes without persistent ST-segment elevation, but relative effects depend on appropriate patient selection. Recent data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines) quality improvement initiative suggests that GpIIb/IIIa antagonists are underused in clinical practice. The relationship between GpIIb/IIIa inhibition and the magnitude of clinical benefit in the setting of acute coronary syndromes is complex. Several key factors should be considered for proper patient selection, including accurate patient risk stratification, incorporation of these agents with an early invasive management strategy and the concomitant use of other anti-thrombotic therapies. Current practice guidelines for the treatment of patients with non-ST-segment elevation acute coronary syndromes support the integration of an early invasive management with optimal pharmacological therapy, including GpIIb/IIIa antagonists.

Non-ST-segment elevation acute coronary syndromes (NSTE ACS), including unstable angina and non-ST-segment elevation myocardial infarction (MI), are responsible for >1 million hospital admissions per year in the US.[1] In the last 30 years, marked advances in our understanding of the pathogenesis of NSTE ACS and the subsequent development of invasively directed management strategies have greatly improved clinical outcomes. Aspirin (acetylsalicylic acid), unfractionated heparin (UFH), low-molecular weight heparin (LMWH), β-adrenoceptor antagonists (β-blockers), thienopyridines (ticlopidine, clopidogrel) and glycoprotein (Gp) IIb/IIIa receptor antagonists now have confirmed clinical benefit in NSTE ACS. Recent data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines) quality improvement initiative demonstrates that many patients without contraindications to GpIIb/IIIa antagonists are not treated with these agents in clinical practice despite their proven clinical benefit and inclusion in the 2000 and 2002 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of patients with NSTE ACS.[1-3] Five key factors appear to influence the magnitude of benefit that may be realised by the addition of GpIIb/IIIa antagonists to standard medical management consisting of aspirin, either LMWH or UFH, β-adrenoceptor antagonists and nitrates: (i) patient risk stratification; (ii) timing of cardiac catheterisation and percutaneous coronary intervention (PCI); (iii) concurrent use of other antithrombotics; (iv) appropriate dose administration of the GpIIb/IIIa antagonist; and (v) choice of GpIIb/IIIa antagonist.

This article reviews the pathophysiology of NSTE ACS and the mechanism of action for GpIIb/IIIa antagonists, the 2002 AHA/ACC and European Society of Cardiology (ESC) guidelines for the treatment of NSTE ACS, and the relevant literature in support of the incorporation of the key considerations in clinical practice.

1. Pathogenesis of Non-ST-Segment Elevation Acute Coronary Syndromes

Typically, NSTE ACS begins with atherosclerotic plaque rupture followed by platelet activation and aggregation, with subsequent thrombus formation and coronary occlusion, followed by distal embolisation and downstream myocardial damage[4,5] (figure 1). Plaque rupture exposes the subendothelial extracellular matrix along the arterial wall. Platelets adhere to the subendothelium by binding class I glycoproteins and are activated in the presence of thrombin, adrenaline (epinephrine) and adenosine diphosphate (ADP). Platelet activation induces a conformational change in the GpIIb/IIIa receptor, stimulating platelet degranulation. Degranulation releases serotonin, ADP and other vasoactive substances precipitating further platelet recruitment and activation. The conformational change in the GpIIb/IIIa receptor stimulates binding of von Willebrand factor and fibrinogen with subsequent platelet aggregation and thrombus propagation.

The important role of platelet activation and aggregation in thrombus formation makes these important targets in the treatment of NSTE ACS. Aspirin has historically been the foundation of antiplatelet therapy in the treatment of NSTE ACS and results in a 51% decrease in the incidence of death or acute MI at 12 weeks.[6] More potent platelet inhibition was achieved with the discovery of the GpIIb/

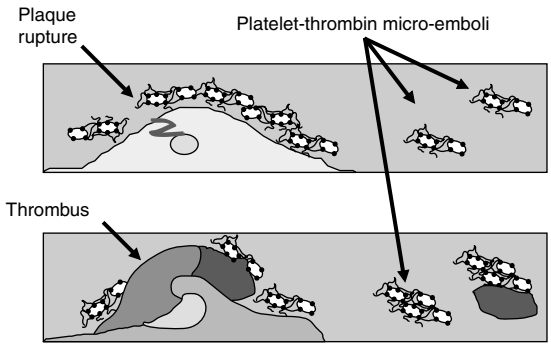

Fig. 1. Pathogenesis of non-ST-segment elevation acute coronary syndromes, including plaque rupture, platelet aggregation and activation, thrombus formation and platelet-thrombin micro-emboli.

Table I. Characteristics of available glycoprotein IIb/IIIa receptor antagonists

Characteristic	Tirofiban	Eptifibatide	Abciximab
Elimination	Renal	Renal	Reticuloendothelial system, renal
Removable by dialysis?	Yes	Yes	No
Binding site	IIb/IIIa receptor B chain	KGD sequence on IIb/IIIa receptor	RGD sequence on IIb/IIIa receptor
Free serum half-life	2h	2.5h	10–20 min
Molecular weight (Da)	495.08	831.96	47 600
Molecule	Peptidomimetic (nonpeptide)	Cyclic peptide containing six amino acids and a mercaptopropionyl residue	Fab fragment of human-mouse chimeric monoclonal antibody
US FDA-approved indications	NSTE ACS	NSTE ACS thrombosis, PCI-related	Thrombosis, PCI-related

NSTE ACS = non-ST-segment elevation acute coronary syndromes; **PCI** = percutaneous coronary intervention.

IIIa receptor and the creation of the first chimeric anti-GpIIb/IIIa receptor monoclonal antibody, abciximab.[7] Several GpIIb/IIIa antagonists have since been developed and are commercially available. These agents differ with regards to binding site, binding affinity, half-life, route of elimination and other pharmacological properties (table I). All GpIIb/IIIa antagonists act by binding the GpIIb/IIIa receptor on the platelet membrane, acting on the final common pathway of thrombus formation and preventing subsequent platelet activation, aggregation and the binding of fibrinogen.

2. Patient Risk Stratification

Patients with NSTE ACS have a wide range of clinical risk. Simple, reliable and accurate methods of risk assessment are available for patient care. Using the PURSUIT (Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial database, Boersma et al.[8] analysed the relationship between baseline characteristics and clinical outcomes in the setting of NSTE ACS and found that the independent baseline predictors of death and recurrent MI within 30 days of a NSTE ACS event are systolic blood pressure, heart rate, ST-segment depression, signs of heart failure and elevation of cardiac biomarkers. From these data the authors developed a simple risk estimation score. Antman et al.[9] developed the TIMI (Thrombolysis In Myocardial Infarction) Risk Score using the baseline characteristics of age ≥65 years, more than three coronary risk factors, prior coronary obstruction, ST-segment deviation, more than two angina events within 24 hours, use of aspirin within 7 days and elevated cardiac markers. The risk score is calculated by the simple sum of these independent predictive variables. They found a high correlation between the number of risk factors and mortality.[9] Subsequent studies have shown that the majority of the predictive power of these models is contained in age >60 years, ST-segment deviation and elevation of cardiac biomarkers. Patients with two of these three features have a 30-day risk of death or nonfatal MI of 13–15%.[10,11]

High-risk patients, including those with both ischaemic ECG changes such as ST-segment depression and elevation of cardiac markers including creatinine kinase (CK), CKMB and troponin I or T, have consistently experienced the most benefit from the addition of a GpIIb/IIIa inhibitor to standard medical therapy.[12] In the CAPTURE (c7E3 Fab AntiPlatelet Therapy in Unstable Refractory angina) study, patients were randomised to either abciximab or placebo before and during PCI for refractory unstable angina. Abciximab therapy reduced 6-month death or nonfatal MI by 60% in patients with elevated troponin but demonstrated no benefit in patients with normal troponin.[13] In a systematic review analysis of the PARAGON-B (Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network), CAPTURE, and PRISM (Platelet Receptor Inhibition in Ischemic Syndrome Management) studies, treatment of NSTE ACS with a GpIIb/IIIa

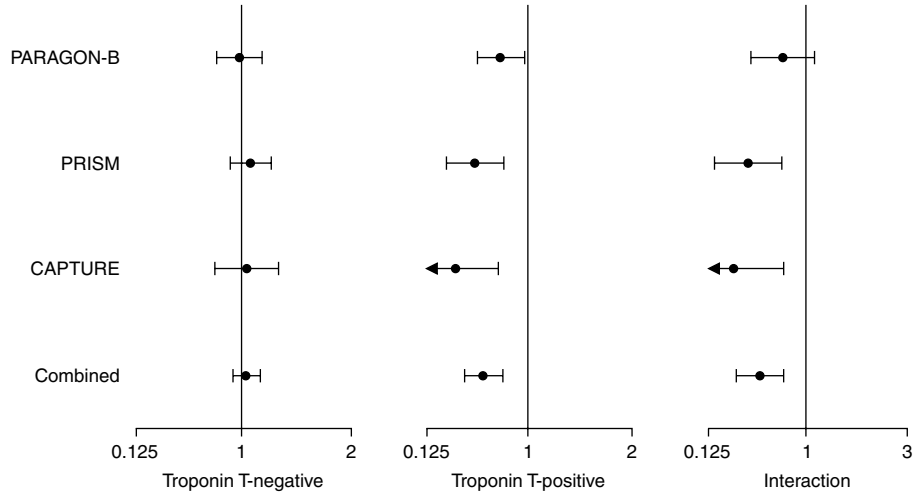

Fig. 2. Odds ratios with 95% CI for death or myocardial infarction among troponin-negative and -positive patients, and for interaction of troponin status with treatment effect for PRISM (Platelet Receptor Inhibition in Ischemic Syndrome Management), CAPTURE (c7E3 Fab AntiPlatelet Therapy in Unstable Refractory angina), PARAGON-B (Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network) and combined trials. Values to the left of 1.0 indicate a benefit of glycoprotein IIb/IIIa receptor inhibition (reproduced from Newby et al.,[14] with permission).

antagonist was associated with a 30–40% reduction in death or MI in patients with an elevated troponin compared with no benefit in patients with a negative troponin[14] (figure 2). In summary, risk stratification using the combination of both elevation of serum troponin and appropriate clinical features of myocardial ischaemia is a simple method for the identification of patients most likely to benefit from the addition of a GpIIb/IIIa antagonist to standard medical management (figure 3 and table II).

3. Timing of Percutaneous Coronary Intervention

A greater magnitude of benefit on clinical outcomes seems to exist among patients treated with a combined approach of early invasive treatment strategy and early GpIIb/IIIa inhibitor initiation. Early intervention is defined differently in individual trials; typically, intervention is considered early if performed within 48–72 hours of symptom onset. The RITA-3 (Randomized Intervention Trial of unstable Angina) demonstrated that an early interventional strategy (within 72 hours of presentation) results in a 33% reduction in the combined endpoint of death, nonfatal MI or refractory angina when compared with conservative medical management in patients presenting with typical anginal chest pain and ECG or cardiac marker changes.[15] The FRISC-2 (FRagmin and Fast Revascularization during InStability in Coronary artery disease) trial showed that an early interventional strategy (within 7 days of presentation) resulted in a decrease in the composite endpoint of MI or death from 12.1% in the non-invasive group to 9.4% in the invasive group at 6 months.[16] Among patients in the TACTICS TIMI-18 (Treat Angina with Aggrastat® and Determine Cost of Therapy with Invasive or Conservative Strategy)[1] trial, an early invasive strategy with revascularisation during the period of GpIIb/IIIa receptor inhibition was associated with a reduction in death, MI or rehospitalisation at 6 months compared with conservative medical management (19.4% vs 15.9%, p = 0.025).[17]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

The 2002 AHA/ACC guidelines for the management of NSTE ACS indicate that an early invasive strategy (catheterisation and PCI, if appropriate, within 48 hours of symptom onset) receives a class IA indication (there is evidence and/or agreement that a given procedure is useful and effective based on several clinical trials) in patients with recurrent angina, elevated troponin I or T, new ST-segment depression, high-risk findings on a stress test, depressed left ventricular function, haemodynamic instability, sustained ventricular tachycardia, recent PCI or prior coronary artery bypass grafting (CABG).[1] They recommend either an early invasive or early conservative approach in the absence of any of these findings (class I indication). The 2002 ESC guidelines state that "Coronary angiography should be planned as soon as possible, but without undue urgency… In most cases coronary angiography is performed within the [first] 48 hours, or at least within hospitalisation period".[18]

Recently the ISAR-COOL (Intracoronary Stenting with Antithrombotic Regimen Cooling-Off) trial showed that pretreatment with antithrombotics for a duration of 3–5 days was associated with a relative risk of repeat MI or death of 1.96 (95% CI 1.01, 3.82) compared with early invasive management with antithrombotic therapy among all patients presenting with NSTE ACS. This suggests that antithrombotic pretreatment should be kept to the minimum duration required to organise cardiac catheter-

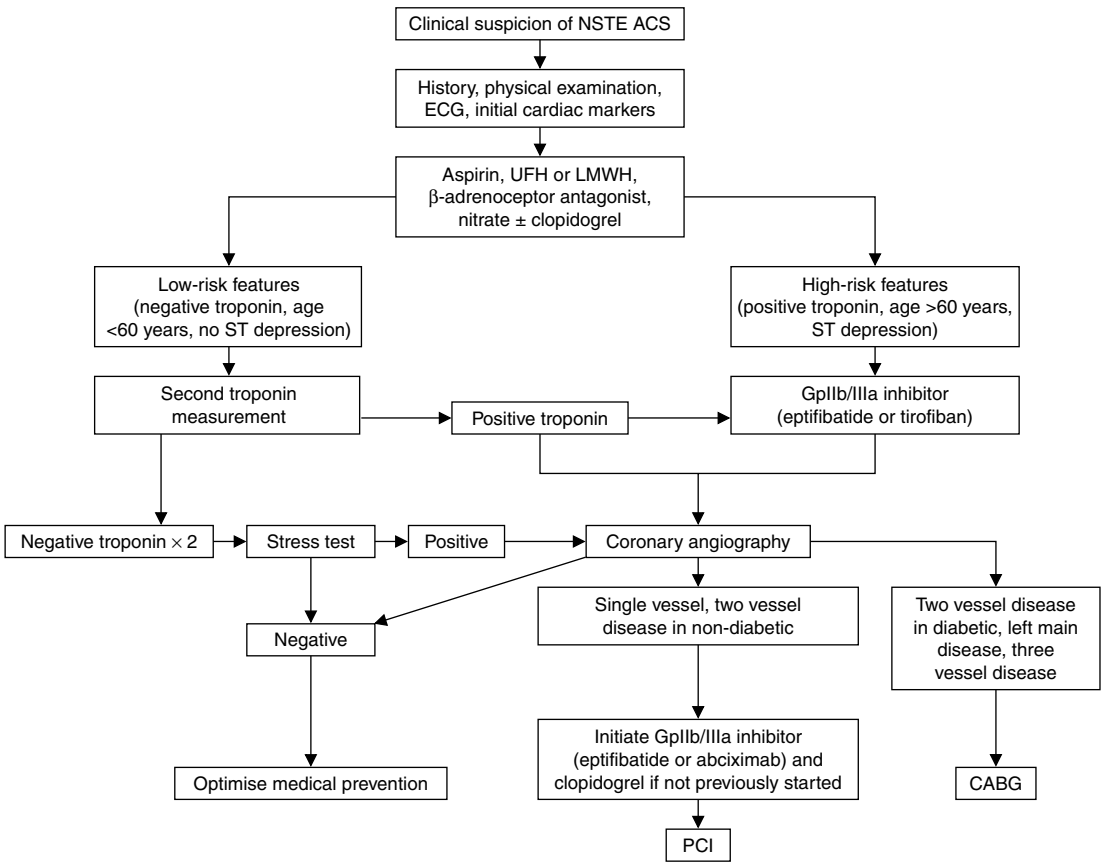

Fig. 3. Non-ST-segment elevation acute coronary syndromes (NSTE ACS) action plan. **CABG** = coronary artery bypass grafting; **Gp** = glycoprotein; **LMWH** = low-molecular weight heparin; **PCI** = percutaneous coronary intervention; **UFH** = unfractionated heparin.

Table II. Contraindications to glycoprotein IIb/IIIa receptor antagonist use

Tirofiban	Eptifibatide	Abciximab
Absolute contraindications		
Intracranial aneurysm	Intracranial aneurysm	Intracranial aneurysm
AV malformation	AV malformation	AV malformation
Active major bleeding	Active major bleeding	Active major bleeding
h/o coagulopathy (e.g. haemophilia)	h/o coagulopathy (e.g. haemophilia)	h/o coagulopathy (e.g. haemophilia)
Intracranial mass	Intracranial mass	Intracranial mass
Stroke in the previous 30 days	Stroke in previous 30 days	Stroke in previous 30 days
h/o haemorrhagic stroke	h/o haemorrhagic stroke	h/o haemorrhagic stroke
Surgery or trauma in the preceding 6 weeks	Surgery or trauma in preceding 6 weeks	Surgery or trauma in preceding 6 weeks
Thrombocytopenia	Thrombocytopenia	Thrombocytopenia
	Renal failure (creatinine >4)	Concurrent dextran therapy
		Murine protein hypersensitivity
		Vasculitis
Relative contraindications		
Concurrent anticoagulation therapy (e.g. with warfarin)	Concurrent anticoagulation therapy (e.g. with warfarin)	Concurrent anticoagulation therapy (e.g. with warfarin)
Breast-feeding, pregnancy	Breast-feeding, pregnancy	Breast-feeding, pregnancy
Age <18 or >75 years	Age <18 or >75 years	Age <18 years
Uncontrolled HTN (SBP >180mm Hg, DBP >110mm Hg)	Uncontrolled HTN (SBP >200mm Hg, DBP >110mm Hg)	Uncontrolled HTN (SBP >200mm Hg, DBP >110mm Hg)
Thrombolytic therapy	Thrombolytic therapy	Thrombolytic therapy
Recent epidural anaesthesia	Recent epidural anaesthesia	Recent epidural anaesthesia
Renal impairment	Renal insufficiency	Abciximab hypersensitivity
ESRD on dialysis	ESRD on dialysis	
Pericarditis		
Aortic dissection		

AV = atrioventricular; **DBP** = diastolic blood pressure; **ESRD** = end-stage renal disease; **h/o** = history of; **HTN** = hypertension; **SBP** = systolic blood pressure.

isation and revascularisation.[19] The implications of the ISAR-COOL trial results remain unclear and the specific timing of diagnostic coronary angiography is still not defined.

Benefit can be obtained from use of GpIIb/IIIa receptor antagonists during the time of medication therapy prior to cardiac catheterisation and percutaneous revascularisation (see figure 4). Although clinical practice is still evolving and a greater proportion of patients with NSTE ACS are being managed with an invasive treatment strategy, most patients are not taken directly to the catheterisation laboratory unless they are unstable after initial medical therapy. Therefore, most patients are treated with GpIIb/IIIa antagonists for 12–24 hours before catheterisation is performed.

In summary, patients presenting with signs and symptoms consistent with high-risk NSTE ACS benefit from the early initiation of GpIIb/IIIa antagonists in combination with early invasive management rather than a conservative medical management approach. The timing of invasive management would be expected to vary greatly based on local practice patterns and available resources.

4. Concurrent Use of Other Anti-Thrombotics

Recently, the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen – Rapid Ear-

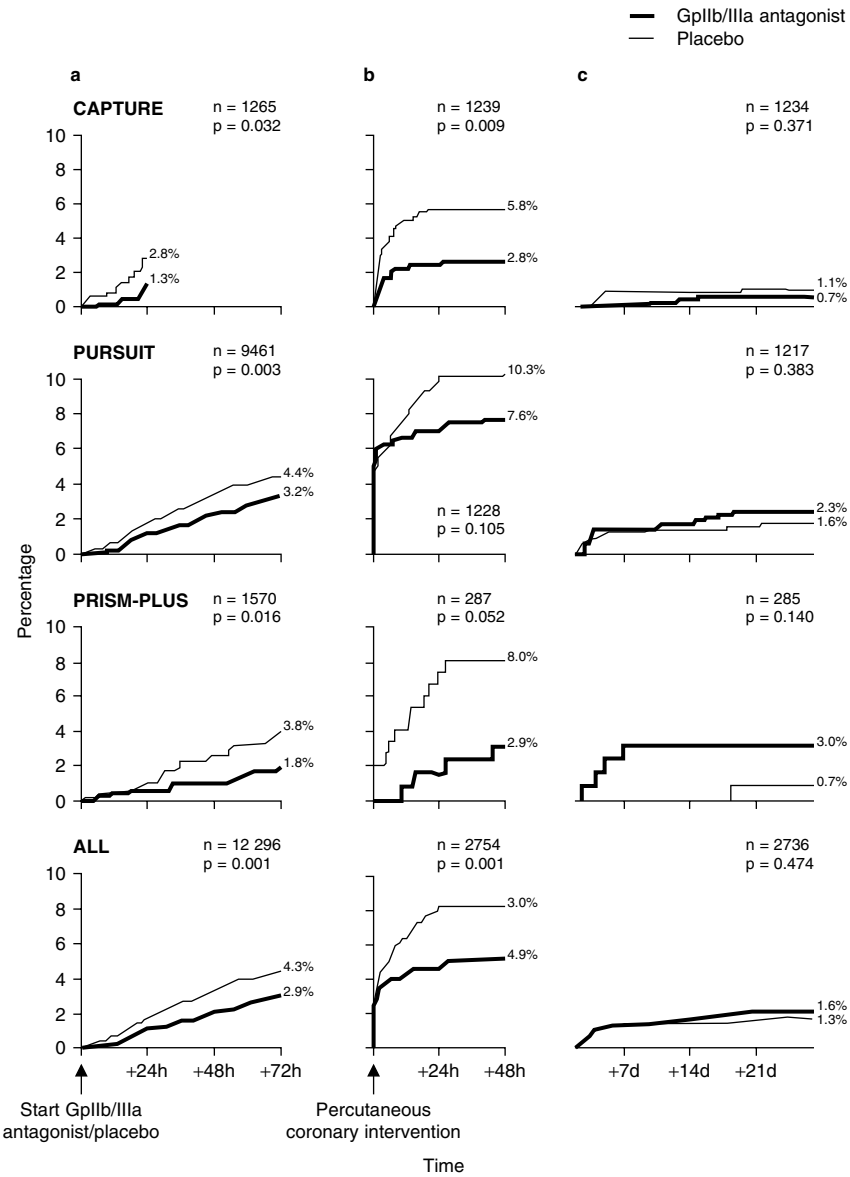

Fig. 4. Kaplan-Meier curves showing cumulative incidence of death or nonfatal myocardial (re)infarction in patients randomly assigned to glycoprotein (Gp) IIb/IIIa inhibition or placebo. Data were derived from CAPTURE (c7E3 Fab AntiPlatelet Therapy in Unstable Refractory angina), PURSUIT (Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) and PRISM-PLUS (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms). (**a**) Event rates during the initial period of pharmacological treatment until the moment of a percutaneous coronary intervention (PCI) or coronary artery bypass grafting, if any. (**b**) Event rates among PCI patients during the 48-hour period after procedure. During and shortly after PCI, all patients were on study medication. (**c**) Event rates in the period starting 48 hours after PCI, during which all patients were off study medication. At the beginning of each period event rates were (re)set at 0%. Any patient still alive contributes to event estimates in each period. In PURSUIT, procedure-unrelated MI was defined as any elevation of creatine kinase (CK)MB above upper limit of normal (ULN). For consistency with CAPTURE and PRISM-PLUS, in present analyses only CK or CKMB elevations 0.23 ULN were considered to be infarctions during medical therapy. In all three trials, procedure-related infarcts were defined by an elevation of CK or CKMB 0.33 ULN (reproduced from Boersma et al.,[20] with permission).

ly Action for Coronary Treatment) trial demonstrated that low-to-intermediate risk patients undergoing elective PCI after pretreatment with clopidogrel 600mg derived no measurable benefit from concurrent treatment with abciximab compared with placebo.[21] There has been no head-to-head comparison of clopidogrel and a GpIIb/IIIa antagonist in the setting of NSTE ACS. The INTERACT (The INTegrilin and Enoxaparin Randomised assessment of Acute Coronary Syndrome Treatment) trial demonstrated that the combination of LMWH and eptifibatide reduced the incidence of nonfatal MI or death compared with the combination of UFH and eptifibatide (5.5% vs 9.0%, p = 0.031), suggesting that the concomitant use of LMWH and GpIIb/IIIa antagonists may be synergistic.[22] There has been debate regarding whether the combination of GpIIb/IIIa antagonists, either LMWH or UFH, aspirin and clopidogrel (quadruple therapy) provides additional benefit to the combinations of (i) aspirin, LMWH or UFH, and clopidogrel, or (ii) aspirin, LMWH or UFH, and GpIIb/IIIa antagonists (triple therapies) in the initial medical treatment of NSTE ACS. Quadruple therapy was used in a subset of patients in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial and the combination appeared to be well tolerated.[23] Although quadruple therapy is commonly used in clinical practice, current ACC/AHA guidelines recommend triple therapy with aspirin, either LMWH or UFH, and GpIIb/IIIa antagonists for initial medical management of NSTE ACS in hospitalised patients in whom catheterisation with possible PCI or CABG is planned.[1] They recommend the combination of aspirin, either LMWH or UFH, and clopidogrel in hospitalised patients in whom a non-interventional approach is planned.[1] There may be synergistic effects in the use of quadruple therapy, including GpIIb/IIIa antagonists, aspirin, either LMWH or UFH, and clopidogrel for up-front treatment of NSTE ACS; however, the combination has not been studied extensively and, therefore, receives a class IIa recommendation in the ACC/AHA guidelines.[1]

Bivalirudin and other direct thrombin inhibitors have been studied extensively in NSTE ACS populations as an alternative to heparin with only modest benefits. Most of this work was done prior to approval of GpIIb/IIIa antagonists. These agents remain attractive alternatives in the setting of NSTE ACS because of their more predictable pharmacodynamics and possible associated reduction in the risk of bleeding. The REPLACE (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events)-2 trial compared the combination of heparin and GpIIb/IIIa antagonists to bivalirudin monotherapy with bailout GpIIb/IIIa use in the setting of PCI.[24] Approximately one-third of the 6002 study patients (≈1000 per group) had NSTE ACS as their indication for PCI. Bivalirudin was shown to be non-inferior to heparin plus GpIIb/IIIa antagonists in the composite outcome of ischaemic complications and was associated with a decreased risk of significant bleeding. The combination of bivalirudin with GpIIb/IIIa antagonists has not been extensively studied. The direct thrombin inhibitors have not been incorporated into routine clinical care or current ACC/AHA or ECS recommendations for management of the NSTE ACS population.

5. Appropriate Dose Administration

Although the threshold level for optimal platelet inhibition has not been established, efficacy of GpIIb/IIIa antagonists is thought to be dependent on high levels of platelet aggregation inhibition (>80%).[25] Achieving >80% platelet inhibition *in vivo* can be challenging as the dose-response relationship is complex, in part because of the induction of intra-platelet GpIIb/IIIa receptor protein expression by the use of GpIIb/IIIa antagonists. Subtherapeutic dose administration of GpIIb/IIIa antagonists has been shown to contribute to a pro-thrombotic, hypercoaguable state, further potentiating rather than preventing the formation of intracoronary thrombus.[26,27] The importance of adequate dose administration may be demonstrated by comparing results of the ESPRIT (Enhanced Suppression of the

Table III. COMPARE (Randomized COMparison of platelet inhibition with abciximab, tiRofiban, and eptifibatide during percutaneous coronary intervention in acute coronary syndromes) trial results

Platelet inhibition (%)	Abciximab (EPISTENT dose regimen)	Eptifibatide (PURSUIT dose regimen)	Tirofiban (PRISM-PLUS dose regimen)	Tirofiban (RESTORE dose regimen)
Drug dose	0.25 mg/kg bolus followed by 0.125 μg/kg/min	180 μg/kg bolus followed by 2 μg/kg/min	0.4 μg/kg bolus followed by 0.1 μg/kg/min	10 μg/kg bolus followed by 0.15 μg/kg/min
At 15min	89	89	83	83
At 30min	91	89	91	92
At 4h	94	96	92	93
At 12h	91	99	91	92

EPISTENT = Evaluation of Platelet IIb/IIIa Inhibitor for Stenting; **PRISM-PLUS** = Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; **PURSUIT** = Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; **RESTORE** = Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis.

Platelet IIb/IIIa Receptor with Integrilin Therapy) trial with the results of the IMPACT II (Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II) trial.[28,29] Using a more aggressive eptifibatide dose administration regimen, ESPRIT demonstrated a 35% relative risk reduction in 30-day death, MI or urgent revascularisation compared with an 18.5% relative risk reduction for these same three variables in IMPACT II.

The dose administration regimens used in early GpIIb/IIIa inhibitor trials were chosen on the basis of results of dose-ranging clinical pharmacology studies using *ex vivo* platelet aggregation assays.[30,31] Further work has demonstrated that the *in vivo* effect of GpIIb/IIIa antagonists may be overestimated during *ex vivo* testing by the use of the anticoagulant sodium citrate in blood specimen tubes.[32] The COMPARE (randomized COMparison of Platelet inhibition with Abciximab, tiRofiban, and Eptifibatide during percutaneous coronary intervention in acute coronary syndromes) trial evaluated the pharmacodynamic profiles of contemporary dose administration regimens of abciximab, eptifibatide and tirofiban used in the pivotal clinical trials of these agents[33] (table III). Using both sodium citrate and RWJ-27755 (PPACK) anticoagulants to measure platelet activation response to a standard 20 μmol/L of ADP, the authors showed that the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting) dose regimen of abciximab (0.25 mg/kg bolus followed by 0.125 μg/kg/min) and the PURSUIT dose regimen of eptifibatide (180 μg/kg bolus followed by 2 μg/kg/min) provided significantly more platelet aggregation inhibition at 15 minutes than the RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis) dose regimen of tirofiban (0.4 μg/kg/min × 30 minutes followed by 0.10 μg/kg/min). These data suggest that early platelet inhibition is inadequate with the RESTORE tirofiban regimen and may explain the excess peri-procedural thrombotic events reported with this regimen compared with abciximab in the TARGET (Do Tirofiban and ReoPro™ Give Similar Efficacy Trial).[34] The TENACITY (a randomized, multicenter, double-blind, abciximab-controlled study to evaluate the efficacy of tirofiban versus abciximab among patients undergoing percutaneous coronary intervention with intracoronary stent placement receiving bivalirudin or heparin) trial is currently being planned to compare a higher dose of tirofiban to abciximab in the setting of PCI to assess this possibility.

6. Choice of Glycoprotein IIb/IIIa Inhibitor

There are currently no available data directly comparing abciximab, eptifibatide and tirofiban in the early medical treatment of NSTE ACS. A review demonstrated that all three agents provide early benefit in the initial medical management of NSTE ACS and also protect against myocardial damage associated with subsequent PCI.[20]

Abciximab, a large molecule monoclonal antibody GpIIb/IIIa inhibitor, has several theoretical advantages to the small molecule GpIIb/IIIa antagonists. Abciximab has been shown to inhibit platelet-leukocyte interactions potentially decreasing the vascular inflammatory processes involved in NSTE ACS.[35] Abciximab also provides a more thorough inhibition of the GpIIb/IIIa receptor within 15 minutes of bolus than the small molecule agents (>95% with abciximab vs ≈80–90% with tirofiban and eptifibatide).[33] Unfortunately, the half-life of abciximab is difficult to predict making subtherapeutic dose administration more likely with abciximab than with eptifibatide or tirofiban, particularly with infusions lasting >4 hours. The GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) IV trial showed no significant benefit to abciximab in the medical management of NSTE ACS[36] and the 2002 ACC/AHA guidelines give a class III recommendation (either not effective or potentially harmful) for the addition of abciximab to standard anti-thrombotic therapy in patients in whom PCI is not planned.[1] Conversely, the TARGET trial showed that abciximab was superior to tirofiban when used at the time of PCI.[34] In summary, abciximab should be used only peri-procedurally in patients not previously started on GpIIb/IIIa antagonists.

Eptifibatide or tirofiban should be used in the initial medical management of NSTE ACS. The addition of eptifibatide or tirofiban to aspirin and either LMWH or UFH in patients with continuing ischaemia, elevated troponin or other high-risk features in patients in whom PCI is not planned receives a class IIa recommendation (conflicting evidence about the usefulness, weight of evidence is in favour of efficacy) in the 2002 ACC/AHA recommendations.[1] Currently, there is no head-to-head comparison of tirofiban and eptifibatide. Eptifibatide reduces 30-day mortality and recurrent MI when used in early medical management of NSTE ACS[37] and in planned PCI.[28] Tirofiban also reduces 30-day mortality and recurrent MI when used in early medical management of NSTE ACS,[38] but has not been shown to reduce these endpoints when used in patients undergoing planned PCI who are not experiencing NSTE ACS.[39] Current ACC/AHA and ESC guidelines recommend use of either eptifibatide or tirofiban for the early medical management of NSTE ACS in patients who are suitable for revascularisation.[1,18]

7. Conclusions

The addition of GpIIb/IIIa antagonists to established therapies for NSTE ACS, such as heparin, aspirin, β-adrenoceptor antagonists and nitrates, provides additional benefit for patients at high risk for recurrent MI or early death. The decision to add a GpIIb/IIIa inhibitor to standard medical management should be made with consideration of several salient points, including appropriate patient risk stratification, suitable choice of GpIIb/IIIa inhibitor, appropriate dose administration and consideration of concurrent anti-thrombotics the patient may be receiving. Since early invasive management is also beneficial in the treatment of NSTE ACS, the optimal therapeutic approach should consist of patient risk stratification followed by the early use of a GpIIb/IIIa antagonist, angiography and revascularization as indicated. Careful consideration of all available data and formulation of an evidence-based treatment plan will maximise potential benefit and provide optimal long-term clinical outcomes.

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References

1. Braunwald E, Antman W, Beasley J, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-summary article. J Am Coll Cardiol 2002; 40: 1366-74
2. Braunwald E, Antman E, Beaslet J, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST segment elevation myocardial infarction: a report of the ACC/AHA Task Force on Practice Guidelines. J Am Coll Cardiol 2000; 36: 970-2
3. Roe M, Ohman E, Pollack C, et al. Changing the model of care for patients with acute coronary syndromes. Am Heart J 2003; 146: 605-12
4. Fuster V, Badimon L, Badimon J, et al. The pathogenesis of coronary artery disease and the acute coronary syndrome. N Engl J Med 1992; 332: 242-250, 310-8
5. Coller B, Anderson K, Weisman H, et al. New antiplatelet agents: platelet GPIIb/IIIa antagonists. Thromb Haemost 1995; 74: 302-8
6. Lewis H, Davis J, Archibald D, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. N Engl J Med 1983; 309: 396-403
7. Coller B, Peerschbacher M, Scudder L, et al. A murine monoclonal antibody that completely blocks the binding of fibrinogen to platelets produces thrombasthenic-like state in normal platelets and binds to glycoproteins IIb and/or IIIa. J Clin Invest 1983; 72: 325-38
8. Boersma E, Pieper K, Steyerberg E, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation: results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation 2000; 101: 2557-67
9. Antman E, Cohen M, Bernink P, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000; 284: 835-42
10. The SYNERGY Executive Committee. The SYNERGY trial: study design and rationale. Am Heart J 2002; 143: 952-60
11. Ohman E, Granger C, Harrington R. Risk stratification and therapeutic decision making in acute coronary syndromes. JAMA 2000; 284: 876-8
12. Heeschen C, Hamm C, Goldmann B, et al. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban: PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. Lancet 1999; 354: 1757-62
13. Hamm C, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels: c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. N Engl J Med 1999; 340: 1623-9
14. Newby L, Ohman M, Christenson R, et al. Benefit of glycoprotein IIb/IIIa inhibition in patients with acute coronary syndromes and troponin T-positive status. Circulation 2001; 103: 2891-6
15. Fox K, Poole-Wilson P, Henderson R, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Lancet 2002; 360: 743-51
16. FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC-II) Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 1999; 354: 708-15
17. Cannon CP, Weintraub WS, Demopoulos LA, et al., for the TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy) – Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001; 344: 1879-87
18. Bertrand M, Simoons M, Fox K, et al. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force on the management of acute coronary syndromes of the European Society of Cardiology. Eur Heart J 2002; 23: 1809-40
19. Neuman F, Kastrati A, Pogatsa-Murray G, et al. Evaluation of prolonged antithrombotic pretreatment ('Cooling-Off' Strategy) before intervention in patients with unstable coronary syndromes. JAMA 2003; 290: 1593-9
20. Boersma E, Akkerhuis M, Theroux P, et al. Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. Circulation 1999; 100: 2045-8
21. Kastrati A, Mehilli J, Schuhlen H, et al. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. N Engl J Med 2004; 350: 232-8
22. Goodman SG, Fitchett D, Armstrong PW, et al., the Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) Trial Investigators. Randomized evaluation of the safety and efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes receiving the glycoprotein IIb/IIIa inhibitor eptifibatide. Circulation. 2003 Jan 21; 107 (2): 238-44
23. Yusuf S, Zhao F, Mehta S, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345: 494-502
24. Lincoff A, Bittl J, Harrington R, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003; 289: 853-63
25. Steinhubl S, Talley D, Braden G, et al. Point-of-Care measured platelet inhibition correlates with a reduced risk of an adverse cardiac event after percutaneous coronary intervention results of the GOLD (AU-Assessing Ultegra) multicenter study. Circulation 2001; 103: 2572-8

26. Cierniewski C, Byzova T, Papierak M, et al. Peptide ligands can bind to distinct sites in integrin alphaIIbbeta3 and elicit different functional responses. J Biol Chem 1999; 274: 16923-32

27. Du X, Plow E, Frelinger A, et al. Ligands 'activate' integrin alpha IIb beta 3 (platelet GP IIb-IIIa). Cell 1991; 65: 409-16

28. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet 2000; 356: 203-44

29. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrelin to Minimise Platelet Aggregation and Coronary Thrombosis-II. Lancet 1997; 349: 1422-8

30. Tcheng J, Harrington R, Kottke-Marchant K, et al. Multicenter, randomized, double-blind placebo-controlled trial of platelet integrin glycoprotein IIb/IIIa blocker Integrilin in elective coronary intervention. Circulation 1995; 91: 2151-7

31. Harrington R, Kleiman N, Kottke-Marchant K, et al. Immediate and reversible platelet inhibition after intravenous administration of a peptide glycoprotein IIb/IIIa inhibitor during percutaneous coronary intervention. Am J Cardiol 1995; 76: 1222-7

32. Phillips D, Teng W, Arfsten A, et al. Effect of Ca2+ on GP IIb-IIIa interactions with Integrelin: enhanced GP IIb/IIIa binding and inhibition of platelet aggregation by reductions in the concentration of ionized calcium in plasma anticoagulated with citrate. Circulation 1997; 96: 1488-94

33. Batchelor W, Tolleson T, Huang Y, et al. Randomized COMparison of platelet inhibition with abciximab, tiRofiban, and eptifibatide during percutaneous coronary intervention in acute coronary syndromes, the COMPARE trial. Circulation 2002; 106: 1470-6

34. Topol E, Moliterno D, Herrmann H, et al. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. N Engl J Med 2001; 344: 1888-94

35. Neumann F, Zohlnhofer D, Fakhoury L, et al. Effect of glycoprotein IIb/IIIa receptor blockade on platelet-leukocyte interaction and surface expression of the leukocyte integrin Mac-1 in acute myocardial infarction. J Am Coll Cardiol 1999; 34: 1420-6

36. The GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early revascularization: the GUSTO IV-ACS randomized trial. Lancet 2001; 357: 1915-24

37. The PURSUIT Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998; 339: 436-43

38. The PRISM-PLUS Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction: platelet receptor inhibition in ischemic syndrome management in patients limited by unstable signs and symptoms. N Engl J Med 1998; 338: 1488-97

39. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Circulation 1997; 96: 1445-53

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