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Antithrombotic Therapies in Primary Angioplasty

Rationale, Results and Future Directions

Giuseppe De Luca and *Paolo Marino*

Division of Cardiology, "Maggiore della Carità" Hospital, Eastern Piedmont University "A. Avogadro", Novara, Italy

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Abstract

Despite the improvement in outcome observed with primary angioplasty compared with thrombolysis, there is still room for improvement. Indeed, despite restoration of optimal epicardial flow in the vast majority of patients, suboptimal myocardial reperfusion is observed in a relatively large proportion. The aim of this article is to provide an up-to-date review of adjunctive antithrombotic therapy for primary angioplasty for ST-segment elevation myocardial infarction (STEMI).

The HORIZONS trial has shown a significant reduction in mortality and major bleeding complications in patients treated with bivalirudin compared with those treated with glycoprotein (GP) IIb-IIIa inhibitors. Thus, bivalirudin may be considered as an alternative strategy to heparin plus GPIIb-IIIa inhibitors in primary angioplasty, especially in patients at high risk for bleeding complications. However, despite the negative results of the FINESSE trial, a large amount of evidence has been observed in favour of early administration of GPIIb-IIIa inhibitors, which should still be considered a reasonable strategy.

Non-responsiveness to aspirin and clopidogrel is relatively common. However, future trials are needed to evaluate whether the routine assessment for non-responsiveness and a consequent change in therapy (to higher dosages of clopidogrel or a switch to another adenosine diphosphate [ADP]-receptor antagonist) may improve clinical outcome. Even though not yet demonstrated, it is conceivable that the greatest benefits of clopidogrel may come from early administration, and that this might be considered as part of a pharmacological facilitation strategy, together with early administration of GPIIb-IIIa inhibitors. As a result of better and faster inhibition of platelet aggregation, further benefits might be expected from the early administration of one of the new oral platelet ADP-receptor antagonists.

As a consequence of the very low mortality currently achieved by primary angioplasty, additional endpoints, such as infarct size and myocardial perfusion, should be considered when exploring the potential benefits of adjunctive antithrombotic therapies in future randomized trials among patients undergoing mechanical revascularization for STEMI.

The treatment of ST-segment elevation myocardial infarction (STEMI) has substantially improved over recent decades, mainly as a result of new pharmacological and/or mechanical reperfusion therapies.[1-5] Primary angioplasty has been shown to provide significant survival benefits compared with thrombolysis. Because atherothrombosis plays a pivotal role in the pathogenesis of myocardial infarction (figure 1),[6] substantial efforts have been made in the last few years to improve antithrombotic therapies, which are an essential treatment component in patients undergoing mechanical reperfusion for STEMI. The aim of this article is to provide a critical, update review of adjunctive antithrombotic therapies for primary angioplasty.

1. Methods of Literature Search

The literature was scanned by formal searches of electronic databases (MEDLINE and CENTRAL) from January 1990 to July 2008 and the scientific session abstracts in *Circulation*, *Journal of the American College of Cardiology*, *European Heart Journal* and *American Journal of Cardiology* from January 1990 to July 2008. Furthermore, oral presentations and/or expert slide presentations were included (searched on the Transcatheter Cardiovascular Therapeutics [http://www.tctmd.com], EuroPCR [http://www.europcr.com], American College of Cardiology (ACC) [http://www.acc.org], American Hospital Association (AHA) [http://www. aha.org] and European Society of Cardiology (ESC) [http://www.escardio.org] websites from January 2002 to July 2008). The following keywords were used: randomized trial, myocardial infarction, reperfusion, primary angioplasty, thrombolysis, half-dose lytics, combotherapy, facilitation, facilitated angioplasty, unfractionated heparin, low-molecular-weight heparin, dalteparin, nadroparin, enoxaparin, reviparin, parnaparin, direct thrombin-inhibitors, bivalirudin, hirulog, hirudin, glycoprotein IIb-IIIa inhibitors, abciximab, eptifibatide, tirofiban, acetylsalicylic acid, aspirin, clopidogrel, ticlopidine, prasugrel, cangrelor, AZD6140, P2Y12 antagonists, resistance, non-responsiveness, bleeding complications, no-reflow phenomenon, inflammation, distal embolization, reinfarction, ischemia time, and time-to-treatment. No language restrictions were enforced.

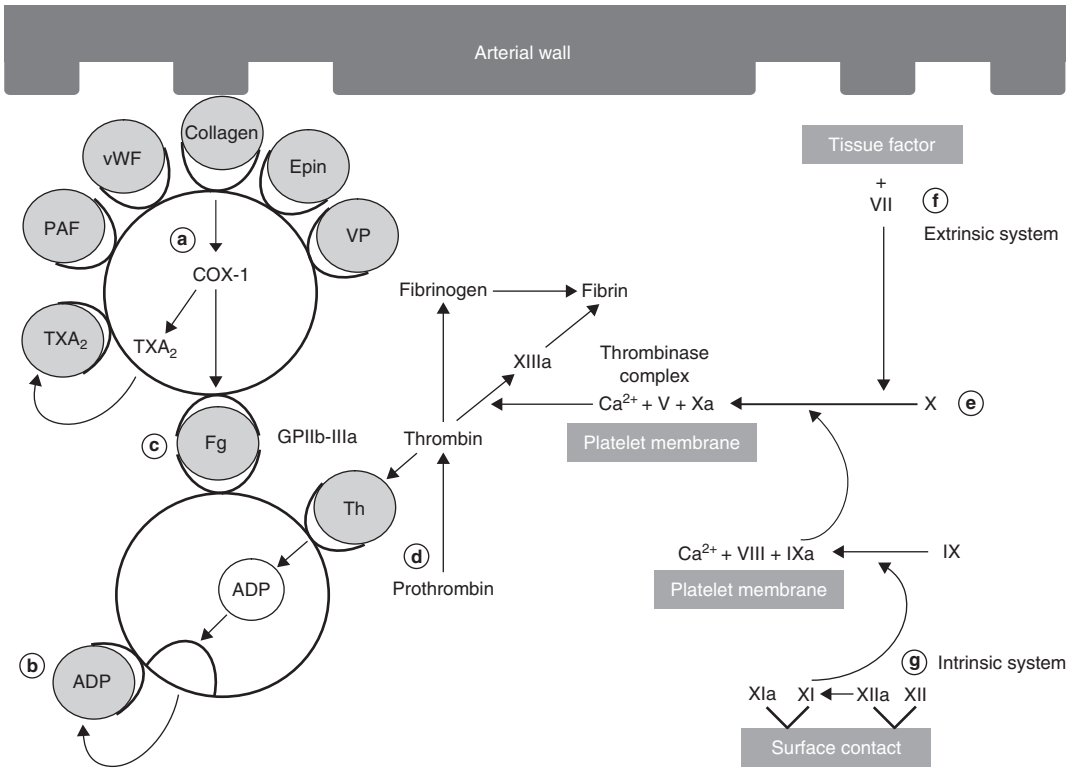

Fig. 1. Platelets, procoagulant activity and coagulation cascade, with several key points at which specific drugs may exert their antithombotic activity: (**a**) acetylsalicylic acid; (**b**) thienopyridines; (**c**) glycoprotein (GP) IIb-IIIa inhibitors; (**d**) direct thrombin inhibitors; (**e**) unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), fondaparinux sodium; (**f**) tissue factor inhibitors; (**g**) UFH, LMWHs. **ADP** = adenosine diphosphate; **COX** = cyclo-oxygenase; **Epin** = epinephrine (adrenaline); **Fg** = fibrinogen; **PAF** = platelet activating factor; **Th** = thrombin; **TXA_2** = thromboxane A_2; **VP** = vasopressin; **vWF** = von Willebrand factor.

2. Rationale for New Antithrombotic Therapies and Strategies

2.1 Incidence and Prognostic Impact of Reinfarction

Several reports have demonstrated the prognostic impact of reinfarction after STEMI in patients treated with thrombolysis or primary angioplasty.[7,8] Despite the greater use observed in the last few years, coronary stenting has not reduced reinfarction compared with balloon angioplasty,[2] and there are even serious concerns about late in-stent thrombosis among patients receiving drug-eluting stents.[9] The incidence of in-stent thrombosis after coronary stenting in primary angioplasty is not so low as commonly believed. In fact, it seems that a greater unrestricted use of coronary stenting is associated with a poorer outcome in terms of reinfarction, particularly when glycoprotein (GP) IIb-IIIa inhibitors are not administered,[10,11] with in-stent thrombosis ranging between 5% and 10%.

2.2 Incidence and Prognostic Impact of Distal Embolization

Despite successful mechanical revascularization, suboptimal reperfusion may occur, resulting in unfavourable outcome.[12-14] In recent years, growing interest has focused on the role of distal embolization as a major determinant of poor reperfusion.

Several studies and clinical reports have implicated distal embolization as a major determinant of infarct size and poor reperfusion after primary angioplasty, and have indicated that distal embolization is a relatively common phenomenon in primary angioplasty. Sakuma and colleagues[15] have shown that the presence of distal embolization is associated with an increase in the perfusion defect and final infarct size of 139% and 70%, respectively, compared with controls. Based on an histological, 3-dimensional reconstruction of the retrieved emboli, Limbruno et al.[16] observed that the embolic load was >2 mm^3 in 15% of patients and >6 mm^3 in 5% of patients, the latter of which could be detectable by angiography. Yip et al.[17] observed in 794 patients undergoing primary angioplasty that the incidence of no-reflow was significantly higher in patients with high thrombus burden. In a recent report, it was observed, using intravascular ultrasound, that plaque volume reduction (an indirect sign of distal embolization when excluding distal or proximal plaque shifting) was 9-fold higher in patients with postprocedural thrombolysis in myocardial infarction (TIMI) perfusion grade 0–2 than those with TIMI perfusion grade 3.[18] Based on the histological analysis of retrieved debris, the EMERALD trial[19] (for full trial names, see table I) showed visible debris in 78% of patients. Henriques et al.[20] reported that the incidence of angiographically detectable distal embolization was 16%, and this was associated with poor reperfusion, larger infarct size and unfavourable 5-year survival compared with patients without angiographic signs of distal embolization. Similar findings were also observed by Napodano et al.[21] in a population of 400 STEMI patients undergoing primary angioplasty.

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 is crucial, especially when the decision to administer adjunctive antithrombotic therapy is undertaken after diagnostic angiography. In a recent analysis by our group,[22] a poor myocardial perfusion outcome was observed more often in small vessels, despite these having less distal embolization compared with larger vessels.

2.3 No-Reflow Phenomenon

In addition to distal embolization and mechanical compression, in the last two decades, interest has focused on the inflammation and spasm of microcirculation as major determinants of no-reflow phenomenon.

Neutrophil activation and accumulation has been demonstrated in damaged myocardium soon after infarct-related artery recanalization.[23,24] In fact, after neutrophil activation, cellular deformability is further attenuated, and this may contribute to leukocyte entrapment in the capillaries, leading to microvascular plugging. Even if capillary leukocyte trapping is prominent in the area of no-reflow, the effects of leukocytes are probably not solely confined to mechanical plugging, but may involve complex interactions with the endothelium and platelets. This interaction is mediated by the selectin family of GP adhesion molecules, including P-, E- and L-selectin, the β2 integrin family and its principal ligand, the endothelial intercellular adhesion molecule-1. Adhesion of activated neutrophils to platelets involves both platelet P-selectin and neutrophil CD18 integrins, further solidifying the association between thrombotic and inflammatory systems.[25-27]

The complement cascade may further modulate these interactions. Activation of neutrophils by the activated factor C5a of the complement system was shown to produce myocardial ischaemia when administered directly into the coronary artery.[28,29] Systemic activation of inflammatory cells might enhance no-reflow, as indicated by the observation that raised serum levels of C-reactive protein are associated with impaired coronary microvascular response to both endothelium-dependent and endothelium-independent vasodilator stimuli[30,31] and with enhanced transcardiac neutrophil activation.[32,33]

Some reports suggest that platelets might interfere with microvascular regulation of coronary blood flow.[34,35] Activated platelets can affect

Table I. Study acronyms and names

Acronym	Full name
ACE	Abciximab and Carbostent Evaluation
ADMIRAL	Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up
APEX-MI	Assessment of PEXelizumab in Acute Myocardial Infarction
ASSENT 3	Assessment of the Safety and Efficacy of a New Thrombolytic Regimen 3
BRAVE-3	Bavarian Reperfusion Alternatives Evaluation 3
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CARESS	Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction
CHAMPION-PCI	A Clinical Trial to Demonstrate the Efficacy of Cangrelor
CHAMPION-PLATFORM	Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition
CLARITY	Clopidogrel as Adjunctive Reperfusion Therapy
COMMIT	ClOpidogrel and Metoprolol in Myocardial Infarction Trial
CURRENT	Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNTs
DISPERSE-2	Dose confIrmation Study assessing anti-Platelet Effects of AZD6140 vs clopidogRel in non-ST-segment Elevation myocardial infarction 2
EMERALD	Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris
EVA-AMI	Abciximab Versus Eptifibatide in Primary PCI for Acute ST-Segment Elevation Myocardial Infarction
ExTRACT-TIMI 25	Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment – Thrombolysis In Myocardial Infarction 25
FATA	Randomized Study on Facilitated Angioplasty with Tirofiban or Abciximab
FINESSE	Facilitated INtervention with Enhanced Reperfusion Speed to Stop Events
GUSTO-V	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
HERO-2	Hirulog Early Reperfusion Occlusion 2
HORIZONS	Harmonizing Outcomes with RevascularIZatiON and Stents in Acute Myocardial Infarction
INTAMI	Integrilin in Acute Myocardial Infarction
ISAR	Intracoronary Stenting and Antithrombotic Regimen
MULTI-STRATEGY	MULTIcentre Evaluation of Single High-Dose Bolus TiRofiban versus Abciximab with Sirolimus Eluting STEnt or Bare Metal Stent in Acute Myocardial Infarction
OASIS 6	Optimal Antiplatelet Strategy for InterventionS 6
On-TIME 2	ONgoing Tirofiban In Myocardial Infarction Evaluation 2
PLATO	PLATelet Inhibition and Patient Outcomes
RAPPORT	ReoPro And Primary PTCA Organization and Randomized Trial
STEEPLE	Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation
STEP-AMI	Safety, Tolerability and Effect on Patency in Acute Myocardial Infarction
STRATEGY	Single High Dose Bolus Tirofiban and Sirolimus-Eluting Stent vs Abciximab and Bare Metal Stent in Myocardial Infarction
TITAN-TIMI 34	Time to Integrilin Therapy in Acute Myocardial Infarction – Thrombolysis In Myocardial Infarction 34
TRITON-TIMI 38	TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel – Thrombolysis in Myocardial Infarction 38
TRANSFER-AMI	Trial of Routine ANgioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction

microvascular resistance by release of constrictive, pro-adhesive and pro-inflammatory factors, in addition to microembolization. In fact, it has been documented that interaction with adhesion molecules prevents microvascular obstruction in experimental models of ischaemia without coronary thrombosis.[36]

The additional affinity of abciximab for non-platelet integrin receptors (the aVb3 and CD11b/18 receptors) explains its anti-inflammatory proper-

ties,[37,38] which may contribute to greater clinical benefits in terms of myocardial reperfusion with abciximab compared with other GPIIb-IIIa inhibitors.

2.4 Interindividual Variability in the Response to Conventional Antiplatelet Therapies

A large interindividual variability has been described in the response to antiplatelet therapies.[39-45] The importance of being able to identify individuals who are aspirin or clopidogrel non-responders[39] (due to incomplete inhibition of thromboxane-A_2 or adenosine diphosphate [ADP]-induced platelet aggregation) is supported by emerging evidence that laboratory aspirin or clopidogrel resistance predicts cardiovascular events.[39-45] The percentage of non-responders ranges between 5% and 50% for aspirin, and between 20% and 30% for clopidogrel,[39-45] depending on the type of test used, which does not allow for a uniform definition of drug non-responsiveness. Several mechanisms have been proposed.[46-64]

Finally, it has been shown that some factors may modulate response to GPIIb-IIIa inhibitors, including platelet count,[65] fibrinogen[65,66] and genetic polymorphisms.[57]

2.5 Limitations of Unfractionated Heparin (UFH)

Despite the low costs, several potential disadvantages of unfractionated heparin (UFH) should be noted: (i) dependence on antithrombin III for inhibition of thrombin activity; (ii) sensitivity to platelet factor 4; (iii) the inability to inhibit clot-bound thrombin; (iv) marked inter-individual variability in therapeutic response; and (v) the need for frequent activated partial thromboplastin time monitoring.

2.6 Bleeding Complications

Aggressive antithrombotic therapy carries a risk of bleeding and blood transfusion. Although the true incidence of bleeding depends on the population studied (i.e. clinical trial vs registry) and the definition used,[67,68] it is clear that bleeding is associated with an increased risk for adverse outcomes, including myocardial infarction and death.[67,69] Therefore, therapies that provide an adequate level of anticoagulation to reduce ischaemia while simultaneously minimizing the risk of bleeding and transfusion have the potential to improve outcomes among patients with STEMI, especially in those patients at higher risk for bleeding complications, such as those with low bodyweight, female sex and impaired renal function.[67-70]

3. Anticoagulation beyond UFH

3.1 Direct Thrombin Inhibitors

Large amounts of thrombin are generated when the coagulation system is activated by tissue factors exposed at the site of plaque disruption.[71] Fibrin-bound thrombin is protected from inhibition by heparin,[72] and remains enzymatically active, amplifying its own generation and promoting further thrombus formation. Bound thrombin also continues to activate platelets through thromboxane-A_2-independent mechanisms that can not be blocked by aspirin.[71,72]

Bivalirudin is a 20-amino-acid synthetic polypeptide analogue of hirudin[73] (table II). Once bound, bivalirudin is cleaved by thrombin, thereby reducing its antithrombotic activity. Peak bivalirudin concentrations are achieved 15–20 minutes after intravenous infusion. In patients with normal renal function, the plasma half-life of bivalirudin is 25–36 minutes. Although it is predominantly eliminated by plasma enzymes (peptidases), approximately 20% of the drug is excreted via the kidneys.[73] Unfortunately, there is no antidote for bivalirudin.

In the largest trial so far conducted with bivalirudin, the HERO-2 trial,[79] 17 073 patients receiving streptokinase for STEMI were randomized to bivalirudin or UFH. This trial showed similar mortality (10.8% vs 10.9%, respectively; $p = 0.85$), but a 30% reduction in reinfarction at 96 hours with bivalirudin (1.6% vs 2.3%; $p = 0.001$). Patients treated with bivalirudin had a significantly higher

Table II. Characteristics of anticoagulation therapies

Characteristic	LMWH[74]	Fondaparinux sodium[75]	Bivalirudin[73]
Route of administration	SC or IV	SC	IV
Target	Factor Xa and thrombin	Factor Xa	Thrombin
Half-life (h)	4	17	0.5
Plasma protein binding	Low	None	Low
Clearance	Renal	Renal	Renal (20%)
Risk of heparin-induced thrombocytopenia	Yes	No	No
Antidote	Partially neutralized by protamine	No	No
Laboratory test	Factor X	Factor X	ACT
Dosage	IV 0.5 mg/kg bolus, followed by 1 mg/kg[76]	2.5 mg[a]	IV 0.75 mg/kg bolus then infusion 1.75 mg/kg/h[78]
Frequency	Twice daily	Daily	Periprocedural

a A periprocedural bolus of heparin is highly recommended.[77]

ACT = activated clotting time; **IV** = intravenous; **LMWH** = low-molecular-weight heparin; **SC** = subcutaneous.

rate of moderate bleeding (1.4% vs 1.1% with UFH; p = 0.05).

Data from the HORIZONS trial have recently been published.[80] In this trial, a total of 3602 STEMI patients undergoing primary angioplasty were randomized to bivalirudin or GPIIb-IIIa inhibitors (abciximab in 49.9% and eptifibatide in 44.4%) plus UFH. Bivalirudin was associated with a significant reduction in overall net clinical outcome (9.3% vs 12.2%; p = 0.006), mainly due to a significant reduction of major bleeding complications (5.0% vs 8.4%; p < 0.0001). Bivalirudin significantly reduced the incidence of cardiac-related mortality by 38% (1.8% vs 2.9%; p = 0.035), despite a higher rate of 24-hour in-stent thrombosis with bivalirudin (1.3% vs 0.3%; p = 0.0009). Data recently presented at the ACC 2008 annual meeting[81] showed that the reduction in the composite endpoint (including bleeding complications) was equally reduced compared with abciximab or eptifibatide, whereas a slightly higher rate of major adverse cardiac events was observed with bivalirudin compared with abciximab (5.7% vs 5.3%), but not to eptifibatide (5.2% vs 5.7%).

Current AHA/ACC STEMI guidelines[77] state that periprocedural bivalirudin may also be used in patients treated previously with UFH (class 1). Pending additional randomized trials comparing bivalirudin with abciximab in high-risk STEMI patients, in our opinion, bivalirudin may be considered as an alternative strategy to heparin plus GPIIb-IIIa inhibitors, especially among patients at high-risk for bleeding complications.

3.2 Low-Molecular-Weight Heparins

Advantages of low-molecular-weight heparins (LMWHs) include (i) a stable and reliable anticoagulation effect that obviates the need of frequent monitoring of coagulation parameters; (ii) high bioavailability (90%) that allows subcutaneous administration; and (iii) a high anti-Xa **:** anti-IIa ratio, producing blockade of the coagulation cascade in an upstream location, which results in a marked decrement in thrombin generation (table II). It should be noted that LMWHs are only partially neutralized by protamine sulfate.[74]

In the ExTRACT-TIMI 25 study,[76] which included a total of 20 506 STEMI patients treated with thrombolysis, enoxaparin, compared with UFH, was associated with a significant reduction in reinfarction (3.0% vs 4.5%; p < 0.001), but not in mortality (6.9% vs 7.5%; p = 0.11), and with a higher risk of major bleeding complications (2.1% vs 1.4%; p < 0.001). The beneficial effects of LMWHs as adjunct to thrombolysis, despite the higher risk of bleedings, have been confirmed in a recent meta-analysis of randomized trials.[82]

To date, no randomized trial has compared LMWHs with UFH in primary percutaneous coro-

nary intervention (PCI). However, the STEEPLE trial[83] has shown, in elective patients, a significant reduction in major bleeding complications with enoxaparin 0.5 mg/kg bolus compared with UFH. In the 2004 AHA/ACC STEMI guidelines,[5] UFH was suggested as the preferred anticoagulation therapy for patients undergoing primary angioplasty.[4] In the 2007 update,[77] no new specific recommendation is provided on the anticoagulation therapy preferred as initial treatment. However, it is recommended (class 1, new recommendation) to continue enoxaparin if it has been administered prior to a procedure (no additional enoxaparin should be given if already administered within 8 hours prior to the procedure, whereas if the last subcutaneous dose was administered at least 8–12 hours earlier, an intravenous dose of 0.3 mg/kg of enoxaparin should be given).

3.3 Factor X Inhibitors

Fondaparinux sodium is a synthetic analogue of the pentasaccharide sequence present in UFH and LMWHs that mediate their interaction with antithrombin. However, it selectively inhibits factor Xa (7-fold higher inhibition than that of LMWHs), without specific inhibition of thrombin activity.[84] In addition, it was shown that fondaparinux sodium may render the clot more susceptible to fibrinolysis induced by alteplase (tissue plasminogen activator). Unlike UFH, most factor Xa inhibitors do not have a known antidote.

The clinical efficacy and safety of fondaparinux sodium in STEMI has been tested in 12 092 STEMI patients enrolled in the OASIS 6 trial.[75] The results of this study showed that fondaparinux sodium is at least as effective and as safe as UFH among non-reperfused patients or those treated with thrombolysis, whereas it should be avoided among patients undergoing primary angioplasty, unless pretreated with UFH. In fact, for fondaparinux sodium versus heparin, there was a trend to harm among 3768 patients treated with primary angioplasty in terms of death and reinfarction at 30 days (6.1% vs 5.1%; p = 0.19), with a higher rate of intracatheter thrombosis (2.2% vs 0%). In addition, fondaparinux sodium was associated with less major bleeding complications, in all patient groups except primary PCI patients.

The observed higher rate of intracatheter thrombosis is explained by the fact that UFH is effective in modulating the contact activation pathway by inactivating factor XIa and, to a lesser extent, factor XIIa through an antithrombin-dependent mechanism. In contrast, pentasaccharides are ineffective in blocking the contact activation pathway that contributes to intracatheter thrombosis.[85]

Current ACC/AHA STEMI guidelines[77] do not provide any specific recommendation on fondaparinux sodium as initial anticoagulation therapy. However, additional periprocedural administration of an anticoagulant possessing anti-IIa activity is recommended (class 1) in the case of prior treatment with fondaparinux sodium.

4. Antiplatelet Therapy beyond Aspirin

4.1 P2Y12 Receptor Antagonists

Platelets contain a large amount of ADP in their storage granules. After initial aggregation, the release of ADP induces activation of additional platelets and reinforces platelet aggregation (figure 1). It has been known for two decades that thienopyridines (ticlopidine, clopidogrel)[86-88] effectively suppress arterial thrombosis. The use of further drugs to inhibit platelet aggregation in addition to aspirin is very important because of the incomplete suppression of platelet aggregation observed after aspirin administration.

Data from the CLARITY trial[89] have shown that, among 3490 STEMI patients, adjunctive clopidogrel therapy to thrombolysis was associated with a better epicardial and myocardial reperfusion, and a significant reduction in 30-day reinfarction (4.1% vs 5.9; p = 0.02). The benefits from early clopidogrel administration were confirmed in the large randomized COMMIT trial,[90] which included 45 852 patients who were treated within 24 hours of symptom onset. The treatment was continued until discharge or up to 4 weeks in hospital. Clopidogrel was associated with a significant reduction in the primary

endpoint (combined death, reinfarction or stroke 9.2% vs 10.1% without clopidogrel; p = 0.003) and death (7.5% vs 8.1%; p = 0.03). The benefits were observed in patients with or without reperfusion therapies (administered in about 50% of patients, mainly thrombolysis). Of interest, both trials showed no increase in the risk of bleeding complications with adjunctive clopidogrel, which is potentially due to the short duration of treatment.

Even though ticlopidine and clopidogrel have a very similar structure, they widely differ in terms of adverse-effect profile and pharmacological properties. Few data have been reported comparing these two drugs. A non-randomized study performed in Zwolle, the Netherlands,[91] compared clopidogrel and ticlopidine in 883 patients undergoing primary angioplasty, and showed no difference in terms of clinical outcome at 1-year follow-up. Similar findings were observed in a small randomized trial by Parodi et al.,[92] which included 133 patients treated by primary angioplasty. However, so far, no study has evaluated the potential benefits in terms of early reperfusion by early clopidogrel administration soon after diagnosis of STEMI in patients undergoing primary angioplasty.

Non-responsiveness to clopidogrel may be observed in up to 30% of patients, and it is associated with a worse prognosis after coronary stenting.[42-48] This issue may be of high clinical relevance, particularly in patients receiving drug-eluting stents, because of a higher risk of late in-stent thrombosis.[9,43] Because of the impact of subacute stent thrombosis on mortality after primary angioplasty,[7,8] non-responsiveness to clopidogrel deserves greater attention. Future randomized trials are certainly needed to identify the optimal strategy to be adopted in these patients, including a higher daily dose (150 mg),[93] switch to ticlopidine[94] or a new ADP antagonist, or adjunctive oral anticoagulation therapy. The CURRENT trial[95] will hopefully provide important data on the benefits of a higher dose of bolus (600 mg) and daily therapy (150 mg) compared with standard bolus (300 mg) and daily dosage (75 mg) of clopidogrel in 14 000 patients with acute coronary syndrome (ACS) undergoing early planned coronary intervention. A subanalysis of the HORIZONS trial, recently presented at the ACC 2008 annual meeting,[96] showed that a 600 mg bolus of clopidogrel was associated with a significant reduction in mortality (1.9% vs 3.1%; p = 0.03) and reinfarction (1.3% vs 2.4%; p = 0.02) at 30 days compared with a standard 300 mg bolus of clopidogrel, and a paradoxically lower incidence of bleeding complications. However, the significant benefits in mortality and reinfarction were not confirmed at multivariate analysis.

Several novel P2Y12 receptor antagonists (table III) have been developed and are currently under investigation to determine whether they can provide better or more rapid antithrombotic effects than clopidogrel, without an increase in bleeding complications.

Prasugrel is an oral thienopyridine. Like clopidogrel, it is a pro-drug, and thus needs to be metabolized via cytochrome P450 in the liver to produce the active metabolite[100,101] that irreversibly inhibits the platelet P2Y12 receptor.[97] However, there is much more efficient *in vivo* generation of the active metabolite of prasugrel than of the active metabolite of clopidogrel.[101] As a result, a prasugrel 60 mg loading dose results in a much more rapid, potent and consistent inhibition of platelet function than a

Table III. Characteristics of P2Y12 antagonists

Drug	Structure	Direct or indirect	Reversible	Route	Frequency	Phase
Ticlopidine[88]	Thienopyridine	Indirect	No	PO	Twice daily	Approved
Clopidogrel[88]	Thienopyridine	Indirect	No	PO	Daily	Approved
Prasugrel[97]	Thienopyridine	Indirect	No	PO	Daily	III
Ticagrelor[98]	ATP analogue	Direct	Yes	PO	Twice daily	III
Cangrelor[98]	ATP analogue	Direct	Yes	IV	Daily	III
PRT060128[99]	Non thienopyridine	Direct	Yes	PO, IV	Twice daily	II

ADP = adenosine triphosphate; **IV** = intravenous; **PO** = oral.

clopidogrel loading dose of 300[97,102] or 600 mg.[103] Furthermore, a maintenance dose of prasugrel 10 mg/day results in a more potent and consistent inhibition of platelet function than the standard clopidogrel maintenance dose of 75 mg/day.[104] A phase II study of prasugrel in humans showed no significant increase in bleedings compared with clopidogrel.[105] However, as a result of the relatively small sample size of the group receiving prasugrel 60 mg followed by 10 mg/day, the study may have been underpowered to detect a statistically significant higher incidence of bleeding complications (2.0% vs 1.2%, prasugrel vs clopidogrel).

In fact, recently published data from the TRITON-TIMI 38 trial[106] have shown that, among 13 608 ACS patients undergoing coronary angioplasty, a 60 mg loading dose and a 10 mg/day maintenance dose of prasugrel, as compared with approved doses of clopidogrel (300 mg loading dose and a 75 mg/day maintenance dose), was better than clopidogrel in reducing the rates of myocardial infarction (7.4% vs 9.7%; $p < 0.001$), urgent target-vessel revascularization (2.5% vs 3.7%; $p < 0.001$) and stent thrombosis (1.1% vs 2.4%; $p < 0.001$), but was associated with a higher risk of major bleeding complications (2.4% vs 1.8%; $p = 0.03$), especially in patients with a history of stroke or transient ischaemic attack, those aged >75 years and those with a bodyweight <60 kg.[106] However, it must be noted that P2Y12 inhibitors were started in the catheterization laboratory or (in the vast majority of patients) soon after PCI. This may have favoured the agent with the fastest onset of action.

Ticagrelor (AZD6140) is another investigational P2Y12 receptor antagonist (table III). To increase oral bioavailability, the structure of ticagrelor was modified from AR-C109318XX.[98] Unlike ticlopidine, clopidogrel and prasugrel, ticagrelor is not a thienopyridine but an adenosine triphosphate analogue, and it is a direct (i.e. no metabolism of a prodrug is required) and reversible P2Y12 receptor antagonist.[98]

Like prasugrel, ticagrelor results in a more rapid onset of action and a greater degree of platelet inhibition than clopidogrel.[107] Data from the DISPERSE-2 study[108] have shown a similar rate of bleeding complications and a more favourable outcome with the ticagrelor than clopidogrel in 990 ACS patients. The ongoing PLATO trial[109] will provide definite data on ticagrelor (90 mg twice daily) versus clopidogrel in more than 18 000 ACS patients.

Cangrelor is an investigational, direct-acting, reversible P2Y12 receptor antagonist (table III).[98] Unlike the previously described orally administered P2Y12 receptor antagonists (ticlopidine, clopidogrel, prasugrel and ticagrelor), cangrelor is administered intravenously, which, together with the rapid reversal of its effects after the end of the infusion, may be potentially advantageous in the PCI setting. Like prasugrel and ticagrelor, cangrelor results in a more rapid onset of action and greater degree of platelet inhibition than clopidogrel, and it has shown no significant increase in bleeding compared with clopidogrel in phase II studies.[110,111] The STEP-AMI trial investigated the use of cangrelor as an adjunct to reduced-dose alteplase during acute myocardial infarction in order to evaluate its safety, tolerability and efficacy in restoring the patency of the infarct-related artery. Preliminary results[112] have shown that cangrelor as an adjunct to thrombolysis (half-dose) improved epicardial and myocardial reperfusion.

Cangrelor is currently in phase III PCI trials: CHAMPION-PCI[113] (cangrelor bolus 30 μg/kg followed by infusion 4 μg/kg/h vs 600 mg clopidogrel) and CHAMPION-PLATFORM[114] (cangrelor bolus 30 μg/kg followed by infusion 4 μg/kg/h vs placebo).

PRT060128 is an investigational, direct-acting, reversible P2Y12 receptor antagonist with a novel structure[99] (table III). It can potentially be administered orally or intravenously, and has completed phase I clinical studies.

Future trials are needed to evaluate whether new P2Y12 receptor antagonists may improve the outcomes of STEMI patients treated by primary angioplasty and whether those intravenously administered should be considered as an alternative strategy or whether they could even add further benefits to the

Table IV. Characteristics of intravenous glycoprotein (GP) IIb-IIIa inhibitors

Characteristic	Abciximab[115]	Eptifibatide[116]	Tirofiban[117]
Type	Antibody	Cyclic peptide	Non-peptide
Molecular weight (Da)	47.600	832	495
Inhibition	Noncompetitive	Competitive	Competitive
Binding	Irreversible	Competitive	Competitive
Platelet affinity	High	Low	Low
Plasma half-life	10–30 min	2.5 h	2 h
Recovery of platelet function	Slow (24–48 h)	Fast (<4 h)	Fast (4–8 h)
Antigenicity	Present	Absent	Absent
Clearance	Platelet binding, unbound substance via proteolytic cleavage	Renal (60–70%), biliary (20–30%)	Renal (98%)
Recommended dosage			
bolus	0.25 μg/kg	180 μg/kg × 2	25 μg/kg
infusion	0.125 μg/kg/min (12 h)	2 μg/kg/min	0.15 μg/kg/min
Studies[a]	RAPPORT,[118] CADILLAC,[119] ADMIRAL,[120] ISAR,[121] Petronio et al.,[122] Petronio et al.,[123] Zorman et al.,[124] Petronio et al.,[125] Lee et al.[126]	INTAMI,[127] TITAN TIMI-34[128]	STRATEGY,[129] On-TIME 2,[130] MULTI-STRATEGY[131]

a See table I for full study names.

use of GPIIb-IIIa inhibitors, particularly among patients undergoing transportation for primary angioplasty, when early treatment with both therapies may significantly improve early reperfusion.

4.2 Glycoprotein IIb-IIIa Inhibitors

GPIIb-IIIa mediates the final stage of platelet activation. Thus, pharmacotherapy that may block this receptor represents a very attractive strategy. The platelet GPIIb-IIIa inhibitors differ markedly in their pharmacokinetics, pharmacodynamics and differential receptor affinities (table IV). Abciximab and the small-molecule GPIIb-IIIa inhibitors (eptifibatide, tirofiban) have separate, distinct binding sites on the GPIIb-IIIa receptor complex.[115-117]

Several randomized trials have been conducted in primary angioplasty, the vast majority of them on abciximab.[3,11,118-126,132-134] In the largest trial, CADILLAC,[119] a total of 2082 patients were randomized to stent or balloon with or without periprocedural administration of abciximab. Abciximab did not improve myocardial perfusion as evaluated by myocardial blush grade and ST-segment resolution.[133] Some benefits in mortality with abciximab were observed in patients undergoing balloon angioplasty only, whereas no benefits were observed in terms of reinfarction. Abciximab did not increase the risk of bleeding complications. However, a major limitation of this study was the relatively low-risk population. In fact, in trials without strict patient selection, as conducted by Antoniucci and colleagues,[11] abciximab was associated with benefits in terms of death and reinfarction. A recent meta-analysis of randomized trials has shown that periprocedural abciximab administration is associated with a significant reduction in mortality and reinfarction, without an increased risk of major bleeding complications.[3] However, data from the BRAVE-3 trial[135] have shown no benefits in infarct size and 30-day mortality with abciximab when a clopidogrel loading dose of 600 mg was administered. Keeping in mind the relationship between the risk profile and mortality benefits of abciximab administration, it may be claimed that absence of benefits would have been expected in a population with a mortality rate <3%, as observed in the BRAVE-3 trial.[135]

Few data have been reported on eptifibatide and tirofiban.[129,131,134,136-139] Steen and colleagues[134] showed in a small randomized trial (53 patients) a

significantly improved epicardial and myocardial perfusion with adjunctive tirofiban. Data from a randomized trial conducted in Zwolle, the Netherlands,[136] have shown that high-dose tirofiban was associated with a better platelet inhibition than abciximab or a standard dose of tirofiban. In the STRATEGY trial[129] no difference in death and/or reinfarction was observed between high-dose tirofiban and abciximab. Data from the MULTI-STRATEGY trial,[131] have shown a similar outcome (non-inferiority) among 745 STEMI patients undergoing primary angioplasty between tirofiban and abciximab in terms of ST-segment resolution (85.3% vs 83.6), death (3% vs 4%) and reinfarction (4.3% vs 3.5%), and no difference in major bleeding complications (2.4 vs 1.6%). An ongoing randomized trial, FATA,[138] will provide further data on the comparison between these two therapies in primary angioplasty.

In the EVA-AMI trial, presented at the AHA 2007 annual meeting,[139] 400 STEMI patients were randomly assigned to periprocedural administration of eptifibatide or abciximab, with similar outcome between the two molecules. The major limitation of the study is that the primary endpoint (ST-segment resolution at 60–90 minutes) was available in only 50% of patients.

Further benefits may be expected with adjunctive intracoronary administration of GPIIb-IIIa inhibitors. A small randomized trial[140] showed that selective intracoronary administration of abciximab distally to the occlusion (through an over-the-wire balloon) was associated with a significant improvement in myocardial perfusion and smaller infarct size. These data have been confirmed in another small randomized trial,[141] which showed that, among 144 STEMI patients, intracatheter administration of abciximab bolus was associated with improved myocardial perfusion and reduced infarct size compared with an intravenous bolus administration.

5. Pharmacological Facilitation

Several randomized trials have been conducted to evaluate the benefits of early administration of GPI-Ib-IIIa inhibitors in patients undergoing primary angioplasty.[124,127,128,142-152] In the On-TIME trial,[143] a total of 507 STEMI patients transferred to a PCI centre were randomized to early, prehospital initiation of tirofiban ('early') or to its initiation in the catheterization laboratory ('late'). Early tirofiban was associated with a better preprocedural TIMI 2–3 flow (43% vs 34%; p = 0.04) and myocardial perfusion (myocardial blush grade 2–3: 30% vs 22%; p = 0.04). However, no benefits were observed in postprocedural TIMI 3 flow, myocardial perfusion, mortality (4.5% vs 3.7%; p = 0.66) and reinfarction (2.4% vs 3.7%; p = 0.43) at 1-year follow-up. Similar results have been observed in the TITAN-TIMI 34 trial, in which 316 STEMI patients were randomized to early or late eptifibatide.[128] Several small randomized trials[110,129,131,136,138] have been conducted with abciximab, and have shown benefits in terms of preprocedural TIMI flow and myocardial perfusion.

Data from the large FINESSE trial have recently been published.[152] In this trial, up to 2500 STEMI patients were randomized within 6 hours of symptom onset to facilitation with abciximab, with or without half-dose lytic therapy or periprocedural abciximab administration. Compared with late administration, early abciximab did not improve either preprocedural TIMI 2–3 flow (26% vs 25%) or 90-day mortality (5.5% vs 4.5%), and had a non-significantly higher risk of major bleeding complications (4.1% vs 2.6%; p = 0.13). Several limitations should be taken into account when interpreting the results of this trial. First, it was prematurely stopped after 4 years because of slow recruitment. Thus, the very low enrolment rate per centre per year certainly led to a selection bias. In addition, despite the study being focused on facilitated PCI, more than 50% of patients were enrolled in primary PCI centres. However, subgroup analyses have shown a trend in benefits in terms of outcome among patients included within the first 3 hours and in high-risk patients.

In support of the benefits from early abciximab administration, data from the Eurotransfer registry were presented at ESC 2007 annual meeting[153] and showed that, among up to 1000 STEMI patients transferred for primary angioplasty, early abciximab

administration improved preprocedural TIMI 3 flow (17.7% vs 8.9%; $p < 0.05$) and was independently associated with better 30-day survival (3.8% vs 5.8%; $p = 0.007$). In addition, in a retrospective analysis from the large APEX-MI trial,[154] early GPIIb-IIIa inhibitor administration was associated with improved preprocedural TIMI 2–3 flow (27.8% vs 21%), postprocedural reperfusion (complete ST-segment resolution 53.9% vs 49.5%) and reduced 90-day mortality (3.2% vs 4.8%) compared with periprocedural administration.

A recent individual patients' data meta-analysis (including 1662 patients) of randomized trials comparing early versus late administration of GPIIb-IIIa inhibitors in primary angioplasty[155] demonstrated significant benefits in preprocedural TIMI flow with all the molecules. However, only abciximab was associated with significant benefits in post-procedural TIMI flow, myocardial blush, distal embolization and survival. Of note, facilitation did not significantly increase the risk of major bleeding complications (3.2% vs 2.9%).

Further evidence of benefits from early administration of GPIIb-IIIa inhibitors (tirofiban) has been observed in the On-TIME 2 trial.[130] In this study, 984 patients were randomized to early, prehospital administration of high-dose tirofiban (25 μg/kg bolus followed by a 0.15 μg/kg/min maintenance infusion) or placebo. Of note, all patients received early high-dose (600 mg) clopidogrel administration. Early tirofiban was associated with improved pre- and postprocedural reperfusion, with reduced mortality (2.3% vs 4.0%; $p = 0.14$).

Thus, despite the negative results of the FINESSE trial,[152] there is evidence of early GPIIb-IIIa inhibitor administration having beneficial effects, and this treatment should still be considered a reasonable strategy, especially in high-risk patients and within the first hours of symptom onset. This is in accordance with ACC/AHA STEMI guidelines, which suggest abciximab should be administered as early as possible (class IIa).[5]

For years, there have been concerns about the combination of thrombolysis and mechanical reperfusion in STEMI because thrombolytic therapy may induce platelet aggregation and impair the results of adjunctive mechanical revascularization.[156] However, the results of trials on adjunctive thrombolytic therapy have been negative.[157-162] These data may be explained by the higher rates of early re-occlusion and re-infarction, potentially due to the low rate of abciximab administration.

The combination of GPIIb-IIIa inhibitors with half-dose lytic therapy has been shown to provide a higher rate of reperfusion and may reduce the risk of thrombotic complications. This strategy may be appealing, particularly when long-distance transportation to a catheterization laboratory is needed.[163] A few small trials have compared combination therapy with upstream GPIIb-IIIa inhibitors alone for PCI,[164-167] and these have shown no benefits in terms of myocardial salvage[146] and clinical outcome, despite the significantly improved preprocedural epicardial recanalization. Data from the FINESSE trial[152] showed that, despite improvement in preprocedural TIMI flow, combination therapy did not confer any benefit in terms of survival, but was associated with a higher risk of major bleeding complications (4.8% vs 2.6%; $p = 0.025$).

The absence of benefits in terms of survival despite improved preprocedural recanalization may depend on (i) relatively late recanalization; and (ii) potential haemorrhagic transformation of the infarction zone with lytic therapy.

It must be recognized that, even though in several randomized trials the time window for enrolment has been restricted to within the first 6 hours of symptom onset, a large proportion of patients did receive pharmacological facilitation after the first 3 hours, when clinical benefits are certainly low, and the risk of bleeding complications outweighs the benefits from early pharmacological reperfusion, because of less myocardium that can be saved and reduced drug effectiveness.

Remarkably, data from CARESS (which included 600 patients)[168] and TRANSFER-AMI (1060 patients)[169] have recently shown the safety and benefits (in terms of reinfarction and recurrent ischaemia) of early routine angiography (within 6 hours) soon after combination therapy (CARESS)

or full-dose lytic therapy (TRANSFER-AMI), without a significant increase in the risk in TIMI major bleeding complications (2.7% vs 2.3% in CARESS, and 4.6% vs 4.3% in TRANSFER-AMI). These data will probably contribute to the modification of current ACC/AHA recommendations[77] and hopefully will promote future trials in order to address whether the type of pharmacological facilitation should be selected according to the time from symptom onset to presentation. In fact, complete reperfusion within the first 2 hours has a high probability of abortion of myocardial infarction, which should still be considered the target in the treatment of STEMI, independent of whether mechanical reperfusion is planned or not.[170]

6. Conclusions and Future Directions

Great efforts have been made in recent years to improve adjunctive antithrombotic drugs for the treatment of patients undergoing primary angioplasty. Thus, with the aim of providing an updated overview of this rapidly progressing field, we conclude that:

1. Early UFH (before transportation or in the cardiac care unit) plus additional periprocedural administration should still be regarded as the gold standard in initial antithrombotic therapy. In fact, in addition to very low cost, UFH has some advantages compared with new anticoagulants. The first is that the anticoagulant effects of UFH can be rapidly and completely neutralized by protamine. This is essential in the face of intraprocedural mechanical complications, such as coronary rupture. Second, UFH is not cleared by the kidneys and therefore is potentially safer than LMWHs or fondaparinux sodium in patients with renal insufficiency. The third advantage is that UFH is effective in modulating the contact activation pathway.[85]
2. Because of undeniable practical advantages, postprocedural initiation of LMWHs or fondaparinux sodium may be considered instead of continuous intravenous infusion of UFH.
3. Aspirin and clopidogrel still represent the cornerstone of oral antiplatelet therapy. Even though not yet demonstrated, it is conceivable that the greatest benefits of clopidogrel may come from early administration, and that this might be considered as part of a pharmacological facilitation strategy, together with early administration of GPIIb-IIIa inhibitors. As a result of better and faster inhibition of platelet aggregation, further benefits might be expected from early administration of new oral ADP-antagonists.
4. Non-responsiveness to aspirin and clopidogrel is relatively common. However, future trials are needed to evaluate whether routine assessment for non-responsiveness to these drugs and change in therapy (either higher dosages or a switch to another ADP-antagonist) may improve clinical outcome, before monitoring antiplatelet therapy can be recommended in the clinical practice.
5. Because of the positive results observed in the HORIZONS trial,[80] bivalirudin may be considered as an alternative strategy to heparin plus GPIIb-IIIa inhibitors, especially in patients at high risk for bleeding complications.
6. Despite the negative results of the FINESSE trial,[156] early abciximab administration should still be considered a reasonable strategy.
7. Future trials are certainly needed to further explore the advantages of new anticoagulation and antithrombotic therapies among primary PCI patients in terms of both efficacy and safety (bleeding complications). Because of the very low mortality currently observed with primary angioplasty, additional endpoints, such as infarct size and myocardial perfusion, should be considered as major endpoints in future randomized trials among patients undergoing mechanical revascularization for STEMI.

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Correspondence: Dr *Giuseppe De Luca*, Division of Cardiology, "Maggiore della Carità" Hospital, Eastern Piedmont University "A. Avogadro", Corso Mazzini 28, Novara, 28100, Italy.
E-mail: giuseppe.deluca@maggioreosp.novara.it