Contemporary use of glycoprotein IIb/IIIa inhibitors

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Summary
Platelet glycoprotein IIb/IIIa inhibitors (GPI) are antithrombotic agents preventing the binding of fibrinogen to GP IIb/IIIa receptors. Thus, GPI interfere with interplatelet bridging mediated by fibrinogen. Currently, three generic GPI with different antithrombotic properties are available for intravenous administration: abciximab, eptifibatide, and tirofiban. The development of oral GPI was abandoned, whereas intravenous GPI were introduced in various clinical settings during the 1990s, yielding substantial benefit in the treatment of acute coronary syndromes, particularly during percutaneous coronary interventions. Results of the many randomised trials evidenced the efficacy of this drug class, though these trials were conducted prior to the emergence of modern oral antiplatelet therapy with efficient P2Y12 inhibitors. Subsequent trials failed to consolidate the strongly favourable impression of GPI, and indications for their use have been more restricted in recent years. Nonetheless, GPI may still be beneficial during coronary interventions among high-risk patients including acute ST-elevation and non-ST-elevation myocardial infarctions, particularly in the absence of adequate pretreatment with oral antiplatelet drugs or when direct thrombin inhibitors are not utilised. Intracoronary GPI administration has been suggested as adjunctive therapy during primary percutaneous coronary intervention, and the results of larger ongoing trials are expected to elucidate its clinical potential. The present review outlines the key milestones of GPI development and provides an up-to-date overview of the clinical applicability of these drugs in the era of refined coronary stenting, potent antithrombotic drugs, and novel thrombin inhibiting agents.

Keywords
Abciximab, acute coronary syndrome, antiplatelet agents, glycoprotein IIb/IIIa inhibitors, percutaneous coronary intervention

Introduction
The discovery of the platelet glycoprotein (GP) IIb/IIIa receptor marked a breakthrough in the understanding of platelet physiology and pharmacotherapy. During the late 1990s, the introduction of specific GP IIb/IIIa inhibitors (GPI) yielded a substantial clinical benefit in the setting of acute coronary syndromes (ACS), particularly during percutaneous coronary intervention (PCI), as verified by several large-scale randomised trials (1–6). Currently, three different drugs are clinically available for intravenous administration: abciximab, eptifibatide, and tirofiban. These drugs differ with respect to pharmacodynamics and pharmacokinetics, including antithrombotic properties (Table 1).

Inhibition of the GP IIb/IIIa receptor and its clinical implications were originally recognised during the investigation of Glanzmann thrombasthenia, an autosomal recessive bleeding disorder characterised by quantitative and/or qualitative defects of the GP IIb/IIIa receptor. During the 1970s an increasing understanding of the receptor was gained, ultimately leading to the development of monoclonal mouse antibodies against GP IIb/IIIa used to induce a transient state of controlled thrombasthenia (7).
cardiac infarction (MI) (9–12). GPI exert their antithrombotic effect by preventing the binding of fibrinogen to adjacent GP IIb/IIIa receptors, thus interfering with interplatelet bridging mediated by fibrinogen (Fig. 1) (13). By this mechanism, the final common pathway of platelet aggregation is blocked. Other adhesive proteins may interact with the receptor (i.e. von Willebrand factor, fibronectin, and vitronectin); however, fibrinogen serves as the primary ligand (8). GPI must maintain ≥80% receptor occupancy to achieve sufficient therapeutic efficacy (14). Such platelet inhibition is particularly important in ACS and PCI, during which platelets adhere and aggregate at sites of plaque rupture and potentially on metallic stent struts.

Pharmacology of GP IIb/IIIa inhibitors

Differences between GPI are outlined in Table 1. Abciximab, the first GPI approved for clinical use, is a non-competitive inhibitor of GP IIb/IIIa. Abciximab is the humanised chimeric Fab-fragment of the monoclonal mouse antibody 7E3 against GP IIb/IIIa (15). Free plasma abciximab is cleared from the circulation within minutes, while platelet-bound drug persists for up to one week depending on the rate of platelet turnover (14). Abciximab cross-reacts with the αβ3 integrin on endothelial cells and smooth muscle cells, as well as the αβ2 integrin (Mac-1) on granulocytes and monocytes (16). Two small-molecule GPI acting specifically on the αβ3-chain of the GP IIb/IIIa complex have been approved for clinical use: eptifibatide (plasma half-life 2.5 hours [h]), an RGD mimic blocking aggregation by occupying the RGD (Arg-Gly-Asp acid) binding site of GP IIb/IIIa, and tirofiban (plasma half-life 2 h), a non-peptide tyrosine derivative also blocking the RGD binding site. Unlike abciximab, eptifibatide and tirofiban are competitive inhibitors of GP IIb/IIIa. Their effect on platelet aggregation is closely related to plasma concentrations and, due to short plasma half-lives, continuous infusion is needed for sustained platelet inhibition (17). Accordingly, the antiaggregatory effect of these drugs decreases within hours after infusion, since recovery of platelet function occurs as soon as the active drug has been renally excreted.

Differences between GPI agents in terms of antiplatelet potency have been reported (18). Furthermore, substantial inter-individual variability in the level of platelet inhibition obtained by GPI has been demonstrated in patients undergoing PCI and may predict cardiovascular events (19).

Oral administration

The breakthrough of GPI was driven by the remarkable results of trials assessing the effect of intravenous agents. In the wake of these results, oral GPI (xemilofiban, orbofiban, sibrafiban, and lotrafiban) were developed and tested against placebo on top of aspirin to investigate a potential role for GPI in long-term secondary prevention. However, in large-scale clinical studies these drugs increased bleeding and thrombosis and generated an excess overall mortality of approximately 30% (20). The excess mortality was not clearly caused by an increase in MIs and was observed despite a reduction in the need for urgent revascularisation, thus arguing against a pure prothrombotic mechanism. Several potential explanations for this disappointing outcome were suggested, including drug toxicity, inadequate drug plasma levels, paradoxical receptor activation, diversity in patient-specific factors (e.g. individual vari-
ation in dose-response), and the lack of concurrent aspirin treatment in some study arms. Thus, GPI were never adopted into clinical practice.

Intravenous administration

Numerous clinical trials have established the clinical benefit of intravenous GP IIb/IIIa inhibition in patients undergoing PCI including non-ST-elevation acute coronary syndromes (NSTE-ACS) and ST-elevation MIs (STEMI). However, many of these trials were conducted prior to the emergence of contemporary antithrombotic agents like clopidogrel and, thus, should be interpreted as such. In addition, new antithrombotic drugs, such as new generation P2Y₁₂ receptor antagonists and anticoagulant drugs, have further challenged the current position of GPI and questioned their relevance in a broad range of clinical settings.

Dosing and administration

Since the first clinical trials, attempts have been made to optimise the dosing regimen of abciximab and, in particular, of the small molecule agents by doubling bolus doses or extending infusion periods. Abciximab is administered as a 0.25 mg/kg bolus dose followed by a 12-h maintenance infusion of 10 μg/minute (min). Dosing is based on the EPIC trial that showed the superiority of bolus abciximab plus infusion as compared with bolus alone (1). In EPILOG, the successor to EPIC, heparin doses were reduced to the currently recommended bolus dose of 70 IU/kg (2). A recent study even showed that withholding abciximab maintenance infusion does not impair platelet inhibition in patients receiving a high loading dose of clopidogrel (21). Abciximab is eliminated through the reticuloendothelial system, including the spleen, and does not require dose adjustment in the setting of renal insufficiency (22). Platelet aggregation returns to baseline after approximately 48 h (17). Recently, intracoronary bolus administration into the infarct-related artery during primary PCI has been investigated as detailed below.

Eptifibatide is administered as a 180 μg/kg bolus dose followed by a maintenance infusion of 2.0 μg/kg/min for 18 to 24 h or until discharge. In the setting of PCI, a second bolus of 180 μg/kg is given 10 min after administration of the first bolus. Current recommendations for dosing are based on the results of the ESPRIT trial that demonstrated the clinical benefit of high-dose versus low-dose epftifibatide (23). These findings were consolidated, and perhaps pharmacologically explained, in the PRIDE study that showed the necessity of high-dose eptifibatide to obtain sufficient GP IIb/IIIa receptor occupancy (24).

Previous recommendations on dosing of tirofiban were based on the RESTORE trial (25); however, they were changed according

<table>
<thead>
<tr>
<th>Table 1: Characteristics of intravenous glycoprotein IIb/IIIa inhibitors. Modified from Brown et al. (85).</th>
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<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>Platelet-bound half-life</td>
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<tr>
<td>Plasma half-life</td>
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<tr>
<td>Drug-to-receptor ratio</td>
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<tr>
<td>Percent of dose in bolus</td>
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<td>Cost</td>
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<td>Specificity/Selectivity</td>
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<tr>
<td>IIb/IIIa</td>
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<tr>
<td>αvβ₃</td>
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<tr>
<td>Mac-1</td>
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<tr>
<td>Anticoagulant properties</td>
</tr>
<tr>
<td>↓ thrombin generation</td>
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<tr>
<td>↑ activated clotting time</td>
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<tr>
<td>Reversibility without platelets</td>
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<tr>
<td>Reversibility with platelets</td>
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<tr>
<td>Route of elimination (22)</td>
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<td>Renal dose adjustment (22)</td>
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CrCl, creatinine clearance.
to the more recent On-TIME 2 trial that demonstrated the clinical benefit of an early high-dose bolus of tirofiban as compared with placebo in STEMI patients (26). In On-TIME 2, tirofiban was administered as a 25 μg/kg bolus dose followed by an 18-h maintenance infusion of 0.15 μg/kg/min.

From the ESPRIT (23) and On-TIME 2 (26) trials it appears that the platelet inhibitory effect of eptifibatide and tirofiban has been optimised by implementing an approximately two-fold increase of the loading dose. The effect of these drugs on platelet aggregation dissipates rapidly once infusion has been discontinued (17). Eptifibatide and tirofiban are renally eliminated and thus require dose adjustments in the setting of renal insufficiency (▶Table 1) (22).

Safety

The large amount of clinical trials involving the use of GPI has revealed an overall acceptable bleeding safety profile of GPI, although depending on the clinical setting in which they are used. Severe non-intracranial bleeding remains a concern when GPI are utilised along with fibrinolytic therapy as demonstrated in GUSTO V (27). In this trial, however, the use of GPI (abciximab) did not confer an increased risk of intracranial haemorrhage. In the setting of PCI, the bleeding risk is acceptable provided that heparin is given in appropriate doses.

When surgery is needed, the reversibility and short half-life of the small molecule agents is advantageous, and they are not considered to confer an increased risk of perioperative bleeding. In contrast, the risk of peri- and postoperative bleeding expectedly increases when abciximab is used.

GPI, in particular abciximab, carry a small risk of thrombocytopenia, which may even occur weeks after administration (28, 29). This should be considered, since GPI-induced thrombocytopenia increases the risk of bleeding (30). Thus, it is recommended to measure platelet counts prior to initiation of GPI treatment and within 2–4 h of abciximab administration and 24 h of eptifibatide and tirofiban administration.

GP IIb/IIIa inhibitors in non-acute patients

GP IIb/IIIa inhibition in the setting of elective and subacute NSTE-ACS PCI has been evaluated in the EPIC, EPILOG, and EPISTENT trials (abciximab), the IMPACT-II and ESPRIT trials (eptifibatide), and in the RESTORE (tirofiban) and TARGET trials (abciximab vs. tirofiban). TARGET is the only trial to directly compare two GPI (31). This study showed superiority of abciximab over tirofiban in patients undergoing PCI. In TARGET, a total of 4,809 elective and NSTE-ACS patients undergoing PCI were randomly assigned to abciximab or tirofiban (low-dose bolus) in addition to aspirin and, in many cases, clopidogrel prior to urgent or elective PCI. Importantly, as the On-TIME 2 trial was yet to be initiated, a low-dose bolus of 10 μg/kg was used in the tirofiban arm of TARGET. Overall abciximab proved superior to tirofiban. Only when analyses were restricted to diabetic patients event rates were equal. Thus, abciximab has been widely used during PCI, especially in patients at particularly high risk of ischaemic complications.

ISAR-REACT (32) tested the effect of abciximab in 2,159 patients undergoing low-risk elective PCI after pretreatment with a high loading dose (600 mg) of clopidogrel. Abciximab provided no reduction in the 30-day incidence of major adverse cardiac events compared with placebo, but caused an increased need for subsequent blood transfusion. Similar results were obtained from 701 diabetic patients in the ISAR-SWEET trial (33). Thus, pretreatment with clopidogrel appears to neutralise the particular benefit of abciximab in diabetic patients undergoing elective PCI that was well documented in earlier studies on GP IIb/IIIa inhibition in clopidogrel naïve patients (31, 34). An ongoing trial is further exploring the role of GPI (eptifibatide) during elective PCI for the treatment of complex lesions (≥2 stents) in patients pretreated with aspirin and clopidogrel (35).

In REPLACE-2 (36), including 2,999 high-risk patients, procedural anticoagulation with bivalirudin, a direct thrombin inhibitor, plus provisional GP IIb/IIIa inhibition proved superior to heparin and systematic GP IIb/IIIa inhibition in reducing bleeding rates while preventing major adverse cardiac events similarly.

Recently, tirofiban has been evaluated in the setting of tailored antiplatelet therapy by the 3T/2R investigators (37). In this study on 1,277 patients undergoing elective PCI, initial screening was performed to identify those with a low platelet response to aspirin, clopidogrel, or both as determined by a point-of-care platelet function test. Low-responders were randomly assigned to tirofiban or placebo on top of aspirin and clopidogrel, the former conferring a significant reduction in peri-procedural MI and major adverse cardiovascular events at 30 days. This benefit was sustained during one-year follow-up (38). Previously, eptifibatide has been shown to enhance platelet inhibition compared to aspirin and clopidogrel alone resulting in reduced myocardial necrosis (39). Another trial, still ongoing, investigates whether administration of a GPI in the catheterisation laboratory will improve clinical outcome in patients on dual antiplatelet therapy (aspirin and clopidogrel) responding inadequately to aspirin. All study participants have stable angina and are undergoing elective PCI (ClinicalTrials.org, NCT01103440).

In the era of P2Y12 receptor antagonists, no clear evidence supports the routine use of GPI during elective PCI, not even in diabetic patients. Previously, GPI were widely used in diabetic patients, but given the results of ISAR-SWEET this strategy is no longer common practice. Thus, when upstream administration of a P2Y12 receptor antagonist is feasible, the European Society of Cardiology (ESC) guidelines state that use of GPI should generally be restricted to bail-out situations caused by coronary thrombus formation, vessel closure, etc. (22). In this setting, most clinicians prefer the use of abciximab (▶Table 2). A recent meta-analysis by Winchester et al. evaluated the use of GPI during elective PCI with stenting from studies of which the vast majority employed pretreatment with thienopyridines. The study concluded that GPI

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provide some clinical benefit by reducing the risk of non-fatal MI without a notable increase in major bleeding, but at the expense of more minor bleeding and a higher rate of thrombocytopenia (30).

Unstable angina and non-ST elevation MI (NSTE-ACS)

A number of large-scale randomised clinical trials have tested the effect of GP IIb/IIIa inhibition in the setting of unstable angina pectoris and NSTE-ACS. The inherent heterogeneity of patients presenting with NSTE-ACS and the diversity of their symptoms renders the risk-benefit outcome more variable than in the case of elective PCI. Some patient subgroups have been shown to receive substantial benefit, whereas others have tended toward more harm from routine use of GPI.

The CAPTURE trial investigated the effect of abciximab in the setting of PCI for high-risk ACS as evidenced by electrocardiographic changes compatible with ischaemia (3). In CAPTURE, patients derived a substantial benefit from abciximab, which could be attributed to a benefit in cardiac troponin-positive patients only. Pursuing a strictly conservative strategy with revascularisation being discouraged during the acute phase, the GUSTO IV-ACS trial yielded results contrasting those observed in CAPTURE (40). Although in GUSTO IV-ACS patients were selected prospectively by use of both cardiac troponin and electrocardiographic changes, abciximab actually led to an increased risk of death at 30 days. Thus, comparison of the results of GUSTO IV-ACS and CAPTURE suggests that the benefit of abciximab in cardiac troponin-positive patients is linked to an invasive strategy. Both studies were conducted prior to the era of routine coronary stenting and before clopidogrel became standard therapy.

The effect of upstream therapy with small-molecule agents was examined in PURSUIT (eptifibatide) and in PRISM-PLUS and PRISM (tirofiban). In PURSUIT (6), a large prospective study encompassing 10,948 patients presenting with either electrocardiographic changes indicative of ischaemia or creatinine kinase MB elevation, eptifibatide proved superior to placebo on top of aspirin and heparin. In PRISM-PLUS (4), tirofiban and heparin were concomitantly administered and compared with heparin alone, and reduced the 30-day death and MI rate. In PRISM (5), the larger successor to PRISM-PLUS, tirofiban was directly compared with heparin on top of aspirin revealing a significant clinical benefit of tirofiban that was, however, not sustained beyond 30 days. Based on these large, but now remote, clinical trials, eptifibatide and tirofiban were previously recommended for upstream therapy in certain cases of NSTE-ACS (41). In NSTE-ACS patients, an early invasive strategy accompanied by intense antithrombotic treatment, including tirofiban, also proved beneficial (42, 43). However, results of the more recent ACUTY-timing (44) and EARLY ACS (45) trials, evaluating the benefit of upstream GP IIb/IIIa therapy in the setting of P2Y12-blockade and refined stenting techniques, showed no benefit. Accordingly, the present ESC guidelines on myocardial revascularisation do not recommend this strategy (22).

Given the observation that clopidogrel pretreatment eradicated most of the benefit of abciximab in elective PCI, the value of abciximab in urgent PCI for ACS seen in CAPTURE had to be re-visited in the era of high-loading dose clopidogrel. Thus, abciximab was re-examined in the recent ISAR-REACT-2 trial (46). In this study, abciximab was administered in the catheterisation laboratory after preloading with clopidogrel in patients subjected to PCI following admission with NSTE-ACS. Abciximab significantly reduced the 30-day primary endpoint and one-year incidence of major adverse cardiac events without increasing the rate of bleeding complications. A pre-specified subgroup analysis revealed that the 30-day benefit of abciximab was confined to patients with elevated cardiac troponin levels.

The more recent EARLY ACS trial (45) investigated the effect of eptifibatide in patients with high-risk NSTE-ACS undergoing angiography and provisional PCI. The study included 9,492 patients presenting within 24 h of symptom debut. Patients were randomly assigned to either early routine eptifibatide (double bolus followed by infusion) or delayed provisional eptifibatide at the time of PCI. The primary endpoint (a 30-day composite of all-cause death, MI, recurrent ischaemia requiring urgent revascularisation, or thrombotic bailout at 96 h) did not differ between groups. Systematic upstream eptifibatide even carried an increased risk of bleeding. However, a recent EARLY ACS substudy showed that the use of routine early eptifibatide, compared with delayed provisional use, may be associated with a lower 30-day ischaemic risk in NSTE-ACS patients also treated with clopidogrel (47).

Bivalirudin has been suggested as an alternative to GPI in patients with ACS. In ACUTY (48), comprising 13,819 patients presenting with NSTE-ACS, systematic GP IIb/IIIa inhibition on top of heparin was compared with bivalirudin plus bail-out GP IIb/IIIa inhibition. Bivalirudin proved non-inferior to heparin plus GP IIb/IIIa inhibition in preventing the ischaemic endpoint, but conferred a significant reduction in the primary endpoint of net clinical outcome including the occurrence of bleeding. Thus, bivalirudin appears an appropriate alternative to GPI, particularly in pa-

Table 2: Common indications for the use of glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention.

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Indications</th>
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<tr>
<td>Non-acute patients</td>
<td>- No pretreatment with aspirin and a P2Y12 receptor antagonist. - Bail-out situations (coronary thrombus formation, vessel closure, etc.), preferably abciximab. - Poor compliance with dual antiplatelet therapy.</td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td>- No pretreatment with aspirin and a P2Y12 receptor antagonist. - High-risk patients (complex lesions, large thrombi, elevated troponin levels).</td>
</tr>
<tr>
<td>STEMI</td>
<td>- High-risk patients (complex lesions, large thrombi, haemodynamically compromised patients).</td>
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<tr>
<td>NSTE-ACS, non-ST-elevation myocardial infarction acute coronary syndromes; STEMI, ST-elevation myocardial infarction.</td>
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patients preloaded with clopidogrel. Some minor uncertainties remain since patients in the non-bivalirudin arms of ACUITY were predominantly treated with small-molecule agents, which may have inferior efficacy compared with abciximab as seen in the ACS patients of the TARGET trial (49). Also, the use of low-molecular-weight heparin in about half of the patients may have impacted the GPI-arm of ACUITY. In an attempt to clarify these issues, the ISAR-REACT-4 trial (ClinicalTrials.org, NCT00373451) is comparing unfractionated heparin plus abciximab to bivalirudin in clopidogrel-pretreated patients undergoing PCI for NSTEMI. ACUITY Timing (44), a substudy of ACUITY, showed no significant advantage of upstream GPI IIb/IIIa inhibition compared with administration in the catheterisation laboratory. In general, upstream administration of GPI is not recommended for the treatment of NSTEMI (22).

Currently, GPI IIb/IIIa inhibition is not recommended as routine therapy for patients with NSTE-ACS (22). The combination of aspirin, clopidogrel, and anticoagulation simply carries a better risk/benefit-ratio and at a lower cost. Results from early ACS (45) highlight the potential risk of bleeding with upstream GPI as part of triple-platelet therapy. However, the use of GPI, in particular abciximab, may be considered in the catheterisation laboratory in high-risk patients or if oral antiplatelet pretreatment has not been given in due time (Table 2). In these cases, though, bivalirudin serves as a strong alternative to GPI due to a lower bleeding risk. Furthermore, the use of GPI is likely to further decrease the advent of the new potent thienopyridine prasugrel and the non-thienopyridine P2Y12 receptor antagonist ticagrelor. Both have proved superior to clopidogrel in TRITON-TIMI 38 (50) and PLATO (51), respectively, and a TRITON-TIMI 38 substudy showed that the superiority of prasugrel was independent of the periprocedural use of GPI (52).

STEMI

Primary PCI is superior to fibrinolysis for the immediate reperfusion of patients with STEMI if performed within a certain time limit (53–55). However, fibrinolysis still plays an important role in the treatment of STEMI in areas with inadequate access to catheterisation facilities. Thus, GPI have been tested as adjunctive therapy to fibrinolysis in the GUSTO V (27) and ASSENT-3 (56) trials. According to these studies, the combination regimen carried an increased bleeding risk and provided no additional benefit in terms of thrombotic complications. Therefore, the combination of fibrinolysis and GPI is not recommended.

In patients undergoing primary PCI, administration of abciximab in the catheterisation laboratory has proved beneficial in a number of trials; RAPPORT (57), ISAR-2 (58), ADMIRAL (59), CADILLAC (60), and ACE (61). Thus, this strategy may be used during coronary interventions except in patients at high risk of bleeding. Recently, the EVA-AMI trial addressed the question whether eptifibatide may serve as an equally effective and less costly alternative to abciximab (62). The study demonstrated the non-inferiority of eptifibatide with respect to the primary endpoint of complete ST-segment resolution one hour post-PCI. Importantly, the power of the EVA-AMI trial (n = 400) did not allow any firm conclusions to be drawn on the potential differences between the two agents in terms of efficacy and safety. Large-scale datasets have added to the evidence of comparability of small-molecule agents to abciximab for primary angioplasty (63).

Smaller studies, including registries, have previously shown promising results of upstream therapy with abciximab at first medical contact (initiated in the emergency room or in the ambulance) (64, 65). Furthermore, a large substudy of the APEX-AMI trial supported the pre-procedural administration of GPI in the setting of STEMI (66). In the APEX-AMI trial, 3,969 of 5,707 patients with STEMI received one of three GPI at the operator’s discretion administered either early (pre-sheath) or late (in-lab). GPI, in particular abciximab, conferred a significant reduction in 90-day clinical outcome when administered pre-procedurally compared with the administration in the catheterisation laboratory or no administration. This benefit was mainly seen in patients with a symptom-to-PCI duration of less than 3 h. However, in the large randomised FINESSE trial abciximab fell short of expectations (67). In FINESSE, 1,624 patients with STEMI were randomly assigned to abciximab administered upstream or in the catheterisation laboratory. No difference in the primary composite endpoint (death from all causes, ventricular fibrillation, cardiogenic shock, and congestive heart failure) was reported, but upstream abciximab increased the risk of bleeding in patients with a symptom-to-PCI time of less than 3 h. Importantly, the administration of GPI in FINESSE was initiated with a notable time delay from symptom onset compared with the studies summarised in the EGYPT meta-analysis (65). The findings of FINESSE also somewhat contrast with those reported in the On-TIME 2 trial (26). In that study, 984 STEMI patients were randomised to tirofiban or placebo administered pre-hospital before being transferred for primary PCI. Importantly, patients were pretreated with a loading dose of clopidogrel in On-TIME 2, but not in FINESSE. The On-TIME 2 study showed improved ST-segment resolution with tirofiban 1 h after PCI. Nevertheless, the study was unable to demonstrate a statistically significant survival benefit or a diminished risk of re-infarction. However, a recent post-hoc analysis of On-TIME 2 revealed a reduction in the incidence of early stent thrombosis (0–30 days) and urgent revascularisation with tirofiban. Early stent thrombosis and prehospital tirofiban were reported as independent predictors of 30-day mortality (68). The FATA trial, however, failed to demonstrate equivalence of high-dose bolus tirofiban to abciximab as adjunctive therapy to primary PCI for achieving effective reperfusion as measured by the incidence of complete ST-segment resolution (69). The MULTISTRATEGY trial compared a high bolus dose of tirofiban (25 mg/kg) plus standard infusion with abciximab in 725 STEMI patients. In this trial, tirofiban proved non-inferior with respect to the primary endpoint of at least 50% ST-segment-elevation resolution at 90 min after PCI (70). An ongoing trial is evaluating whether upstream tirofiban may improve outcome in patients pretreated with prasugrel (ClinicalTrials.org, NCT01336348).
BRAVE-3 (71) tested upstream abciximab against unfractionated heparin (up to 5,000 U) after preloading with a high dose of clopidogrel (600 mg). The BRAVE-3 investigators randomly assigned 800 patients presenting with STEMI within 24 h of symptom onset to either abciximab (bolus followed by a 12-h infusion) or placebo and employed infarct-size imaging by Tc-99m-sestamibi as the primary endpoint. The study failed to show a reduction in infarct size in the abciximab arm. Moreover, no difference was observed in the combined secondary endpoint (30-day incidence of death, myocardial reinfarction, urgent revascularisation, and stroke). There was, however, an increased incidence of thrombocytopenia and a slightly higher rate of TIMI minor bleeding in the abciximab arm.

The HORIZONS-AMI trial (72) tested bivalirudin plus bail-out GP IIb/IIIa inhibition against heparin plus systemic GP IIb/IIIa inhibition in 3,602 patients presenting with STEMI and a symptom onset of less than 12 h. The reduced rate of net adverse clinical events at 30 days reported in the bivalirudin arm was ascribed primarily to a lower bleeding rate and was accompanied by a reduction in mortality. The mortality benefit prevailed and remained statistically significant during three years of follow-up (73). In patients who underwent coronary stent implantation, an excess of acute stent thrombosis within the first 24 h was seen in the bivalirudin arm. Subsequent incidences of stent thrombosis were, however, higher in the GPI arm. Accordingly, during three-year follow-up, the incidence of stent thrombosis was similar between the two arms of HORIZONS-AMI (73). Overall, according to the results of HORIZONS-AMI, bivalirudin is a favorable alternative to abciximab in STEMI patients undergoing primary PCI. This, according to the current ESC guidelines highly recommend (class I) the use of bivalirudin in the setting of STEMI (22). Also in diabetic patients bivalirudin is safe and may reduce cardiac mortality at 30 days and one year (74). Moreover, the ongoing EUROMAX trial (ClinicalTrials.org, NCT01087723) is investigating whether early administration of bivalirudin during transport improves 30-day outcome compared with treatment with unfractionated heparin and optional GP IIb/IIIa inhibition in patients with STEMI intended for primary PCI. The study is expected to provide further insight into the potential of bivalirudin in the management of STEMI patients.

In BRAVE-3, the routine use of abciximab given in the intensive care prior to catheterisation showed no benefit in STEMI patients (71). However, when administered in the catheterisation laboratory this drug remains a justifiable option in high-risk patients (►Table 2). Given the results of FINESSE, the use of GP IIb/IIIa inhibition in facilitated PCI is not recommended at present, although an early use in patients with short symptom duration (<3 h) has been suggested beneficial in the recent APEX-AMI substudy (66) and a meta-analysis (65). Still, bivalirudin is a strong alternative to GP IIb/IIIa inhibition, also in diabetic patients.

Intracoronary administration of GP IIb/IIIa inhibitors

Antithrombotic therapy is an inherent companion to PCI. Nonetheless, PCI is often complicated by distal microembolisation, either catheter-induced or by spontaneous plaque rupture. During recent years, the intracoronary delivery of the first bolus of GPI has been shown to preserve perfusion of the microvascular bed during PCI. This capacity is attributed to the ability of GPI to inhibit platelet aggregation and dissolve newly formed platelet aggregates by displacement of fibrinogen from its receptors (75).

Abciximab has been the predominant agent used to investigate a potential clinical role for intracoronary GPI administration, but a few studies on eptifibatide (76) and tirofiban (77) have recently been carried out as well. In a randomised trial by Thiele et al., patients with STEMI were randomly assigned to a bolus of intravenous or intracoronary abciximab followed by intravenous infusions. The study showed a benefit of intracoronary bolus administration in terms of less microvascular obstruction, reduced infarct size, and improved myocardial perfusion (78). Employing intracoronary eptifibatide administration, the ICE trial supported these findings revealing an excess local GP IIb/IIIa receptor occupancy and improved microvascular perfusion with intracoronary versus intravenous administration (76). However, the recent CICERO trial, a larger randomised trial investigating intracoronary abciximab administration, failed to show any difference with respect to the primary endpoint of restored myocardial reperfusion assessed by complete ST-segment resolution. Conversely, when myocardial reperfusion was assessed by myocardial blush grade or enzymatic infarct size, intracoronary administration proved superior (79). A recent randomised trial employed a clinical endpoint to demonstrate the benefit of intracoronary versus intravenous delivery of abciximab (80). The ongoing INFUSE-AMI trial is evaluating the effect on the infarct size of site-specific abciximab delivered with a local perfusion catheter using bivalirudin as anticoagulation (81). The combination of intracoronary bolus abciximab and aspiration thrombectomy is also being evaluated at present (ClinicalTrials.org, NCT01404507). Another ongoing clinical trial, the AIDA STEMI trial, is expected to provide further information as to whether intracoronary delivery of GPI will translate into a better clinical outcome (82).

At present, no sufficiently powered clinical trials have been undertaken to justify the routine use of intracoronary administration. Moreover, all trials conducted so far compared intracoronary with intravenous administration, which might be of limited clinical relevance given the onward march of bivalirudin.

Key areas for future research

- Novel oral antiplatelet agents like prasugrel and ticagrelor might not provide optimal platelet inhibition within two hours in all clinical settings. Thus, intravenous, and perhaps intracoronary, GPI administration may still serve as an important op-
Intravenous GP IIb/IIIa inhibition during elective PCI is not recommended as routine therapy, but may still be considered when a P2Y₁₂ receptor antagonist has not been given in advance. GP IIb/IIIa inhibition is also worth consideration in bail-out situations even after preloading with clopidogrel in patients undergoing very complex PCI, and if dissection, coronary thrombus formation, troponin-positivity, or other severe complications occur.

In NSTEMI patients, GPI may be considered in the catheterization laboratory in high-risk patients, in patients with significant intracoronary thrombus burden, or in the absence of timely antiplatelet pre-treatment. In these cases, the strongest evidence supports the use of abciximab (22).

Also, in the setting of STEMI, GP IIb/IIIa inhibition should be considered in high-risk patients during PCI. Routine upstream therapy with GPI is not recommended at present.

Current antithrombotic strategies are subject to important changes encouraged by the success of P2Y₁₂ receptor antagonists like clopidogrel and its promising potent successors, prasugrel and ticagrelor. Bivalirudin, a direct thrombin inhibitor, is another important alternative to GPI, especially in patients at increased risk of bleeding undergoing PCI, but also in the setting of NSTE-ACS and, in particular, during primary PCI (22).

Abbreviations
ACS, acute coronary syndrome(s); CAD, coronary artery disease; GP, glycoprotein; GPI, glycoprotein IIb/IIIa inhibitor(s); NSTE-ACS, non-ST-elevation acute coronary syndrome(s); NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

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