**Glycoprotein IIb/IIIa antagonists**

**New developments**

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**Keywords**

Acute coronary syndromes, percutaneous coronary intervention, GP IIb/IIIa antagonists, clinical trials

**Summary**

The role of GP IIb/IIIa antagonists has been focused on patients with acute coronary syndromes undergoing PCI. In the ISAR-REACT 2 study abciximab given in patients with NSTE-ACS undergoing PCI already treated with 600 mg clopidogrel improved 30-day death and reinfarction rate in troponin positive patients. In the large EARLY-ACS trial up-stream therapy with eptifibatide in high risk with NSTE-ACS did not improve clinical outcome. Comparative trials evaluating the effectiveness of abciximab and the small molecules tirofiban did not show any differences between the three GP IIb/IIIa antagonists.

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**Schlüsselwörter**

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**Zusammenfassung**


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**Patients with NSTE-ACS undergoing PCI**

The ISAR-REACT 2 study randomised patients with NSTE-ACS pretreated with 600 mg clopidogrel and scheduled for PCI to...
abciximab or placebo (7). The primary combined endpoint consisted of death and myocardial infarction until 30 days. As depicted in Figure 1 there was a benefit of abciximab in patients with positive troponin, while there was no difference in the event rate in troponin negative patients treated with abciximab or placebo.

These results are line with previous studies with eptifibatide and tirofiban, in which patients with ACS undergoing PCI had a benefit of GP IIb/IIIa inhibitors (8–10). In contrast no benefit of abciximab was seen in patients with NSTE-ACS not undergoing early revascularization (11). Therefore, the use of GP IIb/IIIa antagonists should be restricted to patients with NSTE-ACS with positive troponin treated with early PCI.

**Upstream therapy in patients with NSTE-ACS**

The current practice guidelines support the use of GPIIb/IIIa inhibitors in patient with NSTE-ACS who are undergoing PCI. However, the optimal timing of the initiation of GP IIb/III antagonists and the need to treat all patients (as opposed to provisional use in selected patients) is not clear. As a result practice guidelines differ in their recommendations regarding the early (i.e. soon after presentation) routine use of GP IIb/IIIa antagonists. The 2007 American of Cardiology/American Heart Association Guidelines for the Management of Patients with Unstable Angina (UA) or Non ST-Elevation Myocardial Infarction (NSTE-MI) recommend that patients with high risk features be managed with aspirin and either clopidogrel or a GP IIb/IIIa antagonist prior to angiography (i.e., “early”) (class I) (12). The European Society of Cardiology favours early dual antiplatelet therapy with aspirin and clopidogrel (class I), with the addition of a GP IIb/IIIa antagonist reserved for patients with an elevated troponin, ST-segment depression, or diabetes mellitus (class IIa) (13).

These conflicting recommendations also reflect the undefined role of GP IIb/IIIa antagonists in the modern management of ACS, since most of these data were derived from studies performed before the introduction of intensive medical therapy (i.e., new potent anticoagulants, thienopyridines, statins, and antagonists of the renin-angiotensin-aldosterone axis), the introduction of contemporary interventional devices, and the use of higher-dose regimens of GP IIb/IIIa antagonists. The aim of the EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non-ST-segment Elevation Acute Coronary Syndrome) trial was to evaluate the role and optimal timing of initiation (early routine vs delayed provisional use prior to PCI) of double-bolus + infusion eptifibatide (14) in the contemporary management of high-risk patients with NSTE-ACS (15). The primary efficacy end point was a composite of all-cause mortality, myocardial (re)infarction (MI), recurrent ischaemia requiring urgent revascularization or thrombotic bail-out through 96 hours after randomization. The major secondary efficacy endpoint was the composite of death or (re)MI through 30 days. The median time from presentation to randomization 5.6 hours and the median overall duration of study drug infusion was 36.5 hours. Nearly all (97.5%) patients underwent diagnostic coronary angiography (median 21.4 hours after randomization; 94.6% had angiography after at least 12 hours of study drug infusion).

PCI was performed in 59% of all patients, CABG in 13%, and medical therapy without revascularization in 28%. The strategy of early routine eptifibatide did not reduce the rate of primary endpoint compared with the strategy of early placebo with delayed, provisional use of eptifibatide prior to PCI (9.3% with early eptifibatide vs. 10.0% with early placebo followed by delayed, provisional eptifibatide, OR 0.92, 95% CI 0.80–1.06; p = 0.23). The clinical endpoints at day 30 are shown in Figure 2a. This results strongly suggest that in patients with NSTE-ACS optimally treated with guideline adherent medication an upstream therapy with GP IIb/IIIa antagonists is not recommended.

The results of EARLY-ACS are supported by a substudy of the ACUITY trial (16). In this complex study patients randomised to bivalirudin or heparin plus GP IIb/IIIa antthrombin were subrandomised to immediate or deferred selective initiation of GP IIb/IIIa antagonist therapy. The median time between sub-randomisation and angiography with or without PCI was 4 hours. A PCI was performed in 56.2% of the patients, 95% of the patients in the deferred group received a GP IIb/IIIa during PCI. The results are depicted in Figure 2b.

Taken together the results of EARLY-ACS and ACUTY-timing do not support an upstream therapy of GP IIb/IIIa antagonists before visualization of the coronary anatomy and the decision to perform PCI in patients with NSTE-ACS.

**Abciximab in patients with primary PCI pretreated with 600 mg clopidogrel**

A recent metaanalysis of placebo controlled trial with abciximab in 1101 patients with STEMI and coronary stenting showed a significant reduction in the combined endpoint
of death and myocardial infarction at 3 years (placebo 19.0 vs. 12.9%, \( p = 0.008 \)) (17). However, these trials were performed in patients without an early high loading dose of clopidogrel.

In the BRAVE-3 trial 800 patients with STEMI < 24 hour duration all treated with 600 mg clopidogrel were randomized to placebo or abciximab treatment in the emergency room before primary PCI (18). The primary endpoint infarct size measured with scintigraphy did not differ between placebo and abciximab (16.6% vs 15.7%, \( p = 0.47 \)). There was no difference in the combined clinical endpoint death, reinfarction, stroke or urgent target vessel revascularization at 30 days (3.8% vs. 3.0%, \( p = 0.4 \)) or severe bleeding complications (1.8% vs. 1.8%). These data suggest that in STEMI patients with low risk abciximab has no additional benefit in patients pretreated with 600 mg clopidogrel. However, it has been shown that the benefit of abciximab is mainly dependent on the baseline risk of the placebo group (19). Therefore the results of the BRAVE 3 study may not applicable to a higher risk STEMI population.

Smaller randomized studies have shown an improvement in TIMI patency before primary PCI with the early initiation of GP IIb/IIIa inhibitors. In a metaanalysis (20) of these trials individual patients’ data were obtained from 11 out 13 trials, including 1662 patients (840 patients – 50.5% – randomized to early and 622 patients – 49.5% – to late GP IIb/IIIa inhibitors administration). Early GP IIb/IIIa inhibitors were associated with a significantly better preprocedural TIMI 3 flow (23.0% vs 13.3%, \( p < 0.0001 \)), slightly better in terms of postprocedural TIMI 3 flow (90% vs 87.9%, \( p = 0.18 \)) and myocardial blush grade (49% vs 45.8%, \( p = 0.18 \)), better ST-segment resolution (60.3% vs 54.1%, \( p = 0.02 \)). No difference was observed in terms of major bleeding complications: 3.2% vs 2.9%, Peto OR (95% CI) = 1.13 (0.62–2.06), \( p = 0.68 \), \( p \) het = 0.51.

Early GP IIb/IIIa inhibitors were associated with slight benefits in mortality: 3.7% vs 4.8%, HR (95% CI) = 0.76 (0.48–1.22), \( p = 0.18 \), that were more pronounced with abciximab: 2.6% vs 6.8%, HR (95% CI) = 0.38 (0.17–0.85), \( p = 0.019 \) even at multivariate analysis (\( p = 0.027 \)).

The largest randomized trial so far the FINESSE study did not show any improvement in clinical outcome with the early administration of abciximab compared to abciximab given in the catheterization laboratory after the initial diagnostic angiography (21).

The only randomized trial so far evaluating the prehospital administration of a GP IIb/IIIa inhibitor was the OnTIME 2 study (22). Here patients treated with aspirin, heparin and 600 mg clopidogrel were randomized to pre-hospital high-dose tirofiban or provisional tirofiban during primary PCI. In the provisional group 29% of the patients received tirofiban. The primary endpoint ST resolution was significantly improved in the facilitated group. In addition, total mortality was lower (\( p = 0.044 \)).

These data suggest that in very fresh infarcts with ischaemic times of less than three hours very early upstream therapy with a GP IIb/IIIa antagonist in the pre-hospital phase is beneficial.
Comparison of abciximab and the small molecule GP IIb/IIIa inhibitors in primary PCI

The best studied GP IIb/IIIa inhibitor in placebo-controlled randomized trials in primary PCI is abciximab. However, abciximab is more expensive than eptifibatide and tirofiban and the level of platelet inhibition achieved by the three compounds does not differ substantially. Therefore, several randomized trials were performed comparing abciximab and eptifibatide or tirofiban.

In the EVA-AMI trial 427 with STEMI < 12 hours and planned primary PCI were randomised to double-bolus eptifibatide (n = 226) followed by a 24-hour infusion or single-bolus abciximab (n = 201) followed by a 12-hour infusion (23). The primary endpoint was the incidence of complete ST-segment resolution 60 minutes after PCI, as a measure of myocardial reperfusion. The incidence of the primary endpoint of complete (≥70%) ST segment resolution at 60 minutes after PCI in the intention-to-treat analysis was 62.6% after eptifibatide and 56.3% after abciximab (adjusted difference 7.1%, 95% CI –2.7% –17.0%). All cause mortality 6.2% vs. 4.5% (p = 0.5), reinfarction 0.4% vs. 3.5% (p = 0.03), target vessel revascularization (TVR) 4.4% vs. 6.5% (p = 0.4), the combined point of death, non-fatal reinfarction and TVR 10.6% vs. 10.9% (p = 0.9), stroke 0.5% vs. 0.5% (p = 1.0) after six months and TIMI major bleeding complications 4.0% vs. 2.0% (p = 0.2) after 30 days were observed after eptifibatide and abciximab, respectively.

Thus eptifibatide as adjunct to primary PCI seems equally effective and safe as abciximab with respect to myocardial reperfusion and clinical events.

In two randomized trials tirofiban and abciximab were compared in patients with primary PCI. In both trials there were no significant differences in the primary endpoint ST segment resolution between abciximab and tirofiban or in clinical events (24, 25). A metaanalysis of these trials did not show any significant differences between abciximab and the small molecules in clinical end-points. However, it has to be mentioned that most trials enrolled low risk population, in which the use of GP IIb/IIIa antagonists might be questionable. Thus, a comparative trial of abciximab and the small molecules in higher risk groups would be desirable to determine the equivalence of the compounds.

References