One-year clinical outcomes with abciximab vs. placebo in patients with non-ST-segment elevation acute coronary syndromes undergoing percutaneous coronary intervention after pre-treatment with clopidogrel: results of the ISAR-REACT 2 randomized trial†

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Aims
The aim of this study is to investigate whether the benefit of abciximab in patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACSs) undergoing percutaneous coronary intervention (PCI) after pre-treatment with 600 mg clopidogrel is sustained at 1 year.

Methods and results
We performed 1-year follow-up of 2022 high-risk patients with NSTE-ACS undergoing urgent PCI, who were randomized to abciximab or placebo after pre-treatment with 600 mg clopidogrel in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 trial. The combined incidence of death, myocardial infarction, or target vessel revascularization at 1 year was the primary outcome analysis. At 1 year, the primary outcome was reached in 23.3% of patients allocated to abciximab vs. 28.0% of patients allocated to placebo [relative risk (RR) 0.80, 95% confidence interval (CI) 0.67–0.95, \( P = 0.012 \)]. The combined incidence of death or myocardial infarction was 11.6% in patients allocated to abciximab vs. 15.3% in patients allocated to placebo (RR 0.74, 95% CI 0.59–0.94, \( P = 0.015 \)).

Conclusion
In high-risk patients with NSTE-ACS undergoing a PCI after pre-treatment with 600 mg clopidogrel, adverse events occurred less frequently with abciximab and the early benefit was maintained at 1 year after administration.

Keywords
Abciximab • Acute coronary syndrome • Clopidogrel • Percutaneous coronary intervention

Introduction
According to the recent American Heart Association Heart Disease and Stroke Statistics, acute coronary syndromes (ACS) accounted for approximately 1.6 million hospitalizations including primary and secondary discharge diagnoses in US hospitals in 2004. Patients with non-ST-segment elevation ACSs

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(NSTE-ACs) comprise nearly two-thirds of the overall ACS population. There have been recent advances in percutaneous coronary intervention (PCI) techniques and anti-thrombotic regimen used to treat patients with ACS. Available evidence supports a treatment strategy of earlier angiography and PCI, preferably performed within 24 h of presentation in patients with NSTE-ACS. The use of invasive treatment strategy in these patients has been associated with a constant quest to optimize adjunctive anti-thrombotic therapy. Platelet glycoprotein IIb/IIIa receptor inhibitors, clopidogrel, and their combination have been tested in addition to aspirin and heparin in patients with NSTE-ACS undergoing PCI. Although glycoprotein IIb/IIIa inhibitors are more powerful inhibitors of platelet aggregation than are thiopopyridines, benefit of administration of glycoprotein IIb/IIIa inhibitors to patients treated with thiopopyridines remains unproven, at least in patients with low-to-intermediate risk undergoing PCI. There is limited information regarding the efficacy of combined use of glycoprotein IIb/IIIa inhibitors and clopidogrel in patients with NSTE-ACS undergoing PCI.

The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 trial (ISAR-REACT 2) was a multicentre, randomized, double-blind, placebo-controlled trial that investigated whether abciximab provides incremental benefit in high-risk patients with NSTE-ACS undergoing urgent PCI after pre-treatment with 600 mg clopidogrel at least 2 h before the procedure. The study showed that abciximab reduced the composite 30-day endpoint of death, myocardial infarction, and target vessel revascularization by 25%. However, controversy exists about whether the benefits of abciximab extend beyond the first 30 days after a PCI procedure, especially in patients pre-treated with and receiving long-term thienopyridine for an NSTE-ACS. Thus, we performed 1-year follow-up to investigate whether benefits of abciximab are maintained at 1 year after PCI in high-risk patients with NSTE-ACS enrolled in the ISAR-REACT 2 trial.

Methods

Patients

The ISAR-REACT 2 trial study protocol has been previously published. In brief, the trial was conducted between March 2003 and December 2005 and included 2022 high-risk patients with NSTE-ACS undergoing PCI after pre-treatment with clopidogrel and randomized to receive glycoprotein IIb/IIIa receptor inhibitor abciximab or placebo. Criteria for enrolment included: (i) an episode of angina [with an accelerating pattern or prolonged (>20 min) or recurrent episodes at rest or with minimal effort] within the preceding 48 h and either an elevated troponin T level (>0.03 μg/L) or newly developed ST-segment depression of at least 0.1 mV or transient (<20 min) ST-segment elevation of at least 0.1 mV or new or presumed new bundle branch block; (ii) one or more significant stenosis in a native coronary vessel or venous bypass graft amenable to and requiring a PCI. Exclusion criteria included ST-segment elevation (>0.1 mV in two or more contiguous electrocardiographic leads); haemodynamic instability; pericarditis; life expectancy less than 1 year; increased risk of bleeding; stroke within the preceding 3 months; active bleeding or bleeding diathesis; recent trauma or major surgery within the last month; suspected aortic dissection; oral anticoagulation or the use of glycoprotein IIb/IIIa receptor inhibitors within the last 2 weeks; high blood pressure (>180 mmHg) unresponsive to therapy; a haemoglobin level <100 g/L; haematocrit <34%, or platelet count <100 x 10⁹ or >600 x 10⁹/L; known allergy to any of the study medications; and pregnancy (present or suspected). All patients included in the study provided written informed consent. Institutional Ethics Committee approval was obtained in all participating centres. The study complies with the Declaration of Helsinki.

Details of study protocol

All patients received 600 mg clopidogrel at least 2 h before the PCI, as well as 500 mg aspirin. After a decision to perform PCI was made, patients were randomly assigned in a double-blind manner to receive either abciximab or placebo using sealed opaque envelopes containing the block randomization sequence for each participating centre. Block sizes were not revealed to investigators. Patients in the abciximab arm received a bolus of 0.25 mg/kg weight abciximab, followed by an infusion of 0.125 μg/kg/min (a maximum of 10 μg/min) for 12 h and a 70 U/kg bolus of heparin intravenously. Patients in the placebo arm received a bolus and a 12 h continuous infusion of placebo as well as a 140 U/kg bolus of intravenous heparin. Double blinding was achieved by using identically appearing vials in both study groups. Coronary stents were used in nearly 94% of the patients. Post-interventional anti-thrombotic therapy consisted of aspirin 100–325 mg indefinitely and clopidogrel 75 mg twice daily for the remainder of the hospitalization up to 3 days followed by 75 mg a day recommended for at least 6 months. Other cardiac medications were prescribed at discretion of the patient’s physician. Other details of the study protocol were reported in the primary publication. The local research coordinators collected data and forwarded them to the Data Coordinating Centre.

Follow-up, definitions, and outcomes

The primary outcome of this analysis was the combined incidence of death, myocardial infarction, or target vessel revascularization 1 year after randomization. The composite of death or myocardial infarction was the secondary outcome. Information on deaths was obtained from hospital records, death certificate, or phone contact with relatives of the patient or attending physicians. The diagnosis of myocardial infarction was established in the presence of typical chest pain accompanied by either the appearance of pathological Q-waves in two or more contiguous electrocardiographic leads or elevation of creatine kinase level or its MB isoenzyme to at least three times the upper limit of normal. Target vessel revascularization was defined as coronary bypass surgery or repeat PCI involving the target vessel performed in the presence of restenosis-induced symptoms or signs of myocardial ischaemia. All patients were either seen by their physician or interviewed by phone at 30 days, 6 months, and 1 year after procedure; patients with cardiac complaints underwent a complete clinical, electrocardiographic, and laboratory check-up. All events were adjudicated and classified by an adjudication committee blinded to assigned treatment throughout the interval of follow-up.

Statistical analysis

Data are presented as mean ± standard deviation or as counts or proportions (%). Categorical variables were compared with the χ² test or Fisher’s exact test, when expected cell values were less than 5. Continuous data are compared with the use of two-tailed t-test. Survival analysis was performed by applying the Kaplan–Meier method and log rank test, which allowed the calculation of relative risk (RR) [95% confidence intervals (CIs)] associated with abciximab. Survival
was defined as the interval from randomization until the event of interest. Data for patients who did not have the event of interest were censored at the date of the last follow-up. All analyses were performed using S-plus statistical package (S-PLUS, Insightful Corp., Seattle, WA, USA). A P-value of less than 0.05 was considered to indicate statistical significance.

Results

Baseline characteristics of the patients have been reported in the primary publication. None of the characteristics differed significantly among patients treated by abciximab or placebo.

Clinical outcome at 1 year

Mean follow-up was 355.2 ± 31.1 days in the group treated with abciximab vs. 355.4 ± 31.8 days in the group treated with placebo (P = 0.88), with 2.9% of patients in the abciximab group and 2.3% of patients in the placebo group (P = 0.40) being followed up for less than 11 months.

The 1-year incidence of primary outcome—death, myocardial infarction, or target vessel revascularization—was 23.3% (n = 234) in the abciximab group vs. 28.0% (n = 281) in the placebo group (RR 0.80, 95% CI 0.67–0.95, P = 0.012; Figure 1). The combined incidence of death or myocardial infarction was 11.6% (n = 117) among patients treated with abciximab vs. 15.3% (n = 154) among patients treated with placebo (RR 0.74, 95% CI 0.59–0.94, P = 0.015) (Figure 2). There were 45 deaths among patients who received abciximab and 49 deaths among patients who received placebo (1-year incidence 4.5 and 4.9%, respectively, RR 0.91, 95% CI 0.61–1.37, P = 0.66) (Figure 3). Target vessel revascularization was required in 137 patients (13.2%) who received abciximab vs. 164 patients (16.2%) who received placebo (RR 0.83, 95% CI 0.67–1.02, P = 0.07) (Table 1); it was coronary artery bypass surgery in 10 patients in the abciximab group and 16 patients in the placebo group (1.0 vs. 1.6%, P = 0.23).

In the ISAR-REACT 2 trial, three subsets of patients had been pre-specified: increased troponin level at baseline (>0.03 μg/L), presence of diabetes, and duration of clopidogrel pre-treatment. In the current study, the efficacy of abciximab was also assessed in subsets of patients according to sex or age younger or older than 67 years (median age). The 1-year incidence of the primary outcome and the RR related with the assignment to abciximab therapy or placebo in the entire group of patients and pre-specified groups are shown in Figure 4. The effect of abciximab was statistically significant in younger patients (<67 years of age), men, non-diabetic patients, and those with a clopidogrel loading interval of >3 h. No significant interaction with abciximab regarding the primary outcome for any of the analysed variables was observed. The combined incidence of death or myocardial infarction was also assessed in various subgroups as well (Figure 5). There was a significant interaction between age and abciximab regarding the composite of death or myocardial infarction, demonstrating a preferential beneficial effect of abciximab in younger patients. A trend for an interaction between sex and abciximab, disclosing a more favourable effect in men in reducing the composite of death or myocardial infarction, was also observed (Figure 5).
Abciximab effect and troponin level

Baseline elevated troponin (>0.03 μg/L) was observed in 1049 patients (513 patients received abciximab and 536 patients received placebo). The remaining 973 patients (499 patients received abciximab and 474 patients received placebo) had troponin levels of ≤0.03 μg/L. One-year outcomes in the subgroups with and without elevated troponin are shown in Table 2.

Among patients with an elevated troponin, the 1-year incidence of the primary outcome was 28.6% in the abciximab group vs. 33.3% in the placebo group (RR 0.82, 95% CI 0.66–1.02, \( P = 0.07 \)); among patients without an elevated troponin, the 1-year incidence of the primary outcome was 17.8% in the abciximab group vs. 22.0% in the placebo group (RR 0.79, 95% CI 0.59–1.05, \( P = 0.10 \)). The combined incidence of death or myocardial infarction was 17.2% in the abciximab group vs. 22.1% in the placebo group (RR 0.76, 95% CI 0.58–0.99, \( P = 0.047 \)) among patients with an elevated troponin and 5.8% in the abciximab group vs. 7.7% in the placebo group (RR 0.76, 95% CI 0.49–1.24, \( P = 0.27 \)) among patients without an elevated troponin. The estimates (derived by the Kaplan–Meier method to account for censored data) of individual components of the primary outcome are shown in Table 2. Myocardial infarction in patients with an elevated troponin and target vessel revascularization in patients without elevated troponin generated most of the difference in favour of abciximab in the incidence of the primary outcome at 1 year.

**Discussion**

In this study, we assessed the 1-year clinical outcome of patients enrolled in the ISAR-REACT 2 trial, in which abciximab was compared with placebo in high-risk patients with an NSTE-ACS undergoing PCI after pre-treatment with 600 mg clopidogrel. The main finding is that the beneficial effects of abciximab observed at 30 days are maintained 1 year after PCI procedure. The 1-year composite of death, myocardial infarction, or target vessel revascularization was lower in the abciximab group than in the placebo group.
vessel revascularization was reduced by 20% among patients who received abciximab when compared with patients who received placebo. An analysis of survival curves reveals that benefit by abciximab in the overall population had already been secured within the first 30 days. The parallel course of survival curves depicting the incidence of events in groups with abciximab or placebo beyond the 30-day time point shows that initial benefits of abciximab over placebo are kept relatively constant and thus are maintained up to 1-year of follow-up. Although the 30-day risk was significantly reduced by abciximab only in patients with an elevated troponin level, the present analysis shows that both patients with and without an elevated troponin level appear to benefit from abciximab at 1 year in terms of major adverse cardiac events.

Separate analyses showed that all three components of the primary outcome—death, myocardial infarction, or target vessel revascularization—were reached less often among patients assigned to abciximab than placebo by 1 year after PCI procedure. Furthermore, the subgroup analysis showed that abciximab use was associated with risk reduction in several subgroups of patients. However, the lack of a significant interaction between variables of interest and abciximab regarding 1-year incidence of major adverse cardiac events supports a relatively consistent beneficial effect of abciximab across subgroups.

Table 2: One-year outcome according to troponin level

<table>
<thead>
<tr>
<th></th>
<th>Abciximab</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>With elevated troponin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>513</td>
<td>536</td>
<td>—</td>
</tr>
<tr>
<td>Death, myocardial infarction, or TVR</td>
<td>146 (28.6)</td>
<td>178 (33.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Death or myocardial infarction</td>
<td>88 (17.2)</td>
<td>118 (22.1)</td>
<td>0.047</td>
</tr>
<tr>
<td>Death</td>
<td>34 (6.6)</td>
<td>36 (6.7)</td>
<td>0.95</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>65 (12.7)</td>
<td>90 (16.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>TVR</td>
<td>71 (13.8)</td>
<td>83 (15.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>Without elevated troponin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>499</td>
<td>474</td>
<td>—</td>
</tr>
<tr>
<td>Death, myocardial infarction, or TVR</td>
<td>88 (17.8)</td>
<td>103 (22.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Death or myocardial infarction</td>
<td>29 (5.8)</td>
<td>36 (7.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Death</td>
<td>11 (2.2)</td>
<td>13 (2.7)</td>
<td>0.58</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>23 (4.6)</td>
<td>24 (5.1)</td>
<td>0.74</td>
</tr>
<tr>
<td>TVR</td>
<td>66 (13.2)</td>
<td>81 (17.1)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Data are numbers of patients (%). Percentages are Kaplan–Meier estimates. TVR, target vessel revascularization.
at 1 year after PCI procedure. With regard to the 1-year incidence of the composite of death or myocardial infarction (ischaemic complications), patients with an elevated troponin level at the time of PCI, as well as those with rest pain and ST-segment shifts without an elevated troponin level, appear to benefit from abciximab. In patients with an elevated troponin, the use of abciximab was associated with a reduction in the incidence of myocardial infarction; in patients without elevated troponin, the use of abciximab was associated with a reduction in the incidence of target vessel revascularization. However, as we have no detailed information on urgent and non-urgent revascularization procedures beyond 30 days from the index procedure, we cannot offer a clear-cut answer whether this impact of abciximab on target vessel revascularization reflects a preferential reduction in the rate of urgent revascularizations, as previously demonstrated. Finally, because a subgroup analysis suffers from a limited number of patients/events, the possibility that preferential reduction in the rate of target vessel revascularization in patients without an elevated troponin level could be a chance finding cannot be excluded.

Large-scale studies have confirmed the ability of glycoprotein IIb/IIIa receptor inhibitors to reduce the incidence of major adverse cardiac events in patients undergoing PCI. Durable benefit of glycoprotein IIb/IIIa receptor inhibitors at 6 months and 1 year after coronary stenting has also been reported. The uniqueness of the present findings relates to two observations: in high-risk patients with NSTE-ACS undergoing a PCI after pretreatment with 600 mg clopidogrel, the benefit of abciximab seen at 30 days extended up to 1 year; and patients with NSTE-ACS presenting with rest pain and ST-segment shifts, but without an elevated troponin and pre-treated with 600 mg clopidogrel, seem to benefit from abciximab within the first year of follow-up after a PCI procedure. In contrast, the impact of abciximab in low-to-intermediate risk patients undergoing PCI after pretreatment with 600 mg clopidogrel has been evaluated, and no clinically measurable benefit of abciximab either in the 30-day or 1-year outcomes has been reported. The present study, taken together with earlier studies, suggests that powerful antithrombotic activity is required in high-risk patients with NSTE-ACS.

The current study supports the finding that the benefit of abciximab in patients with NSTE-ACS undergoing PCI is sustainable at 1 year. Other studies have observed a late incremental benefit of abciximab in patients undergoing a PCI. The results of subgroup analyses, however, should be interpreted with caution, because they are subject to the influence of limited power and multiple testing. Obviously, they need confirmation from specifically designed studies in the future. Further analyses are required to clarify whether there is an interaction between abciximab and type of stent, i.e. bare metal or drug-eluting stents with regard to later ischaemic events (myocardial infarction potentially due to stent thrombosis) or target vessel revascularization (potentially due to restenosis).

In conclusion, in patients with NSTE-ACS undergoing PCI after pre-treatment with 600 mg clopidogrel, the beneficial effects of abciximab in the reduction of major adverse cardiac events are maintained at 1 year after procedure.

**Conflict of interest:** A.K. and M.S. reports receiving lecture fees from Bristol-Myers Squibb, Lilly, and Sanofi-Aventis; P.B.B. reports having received lecture fees from Schering Plough and CME companies supported by Bristol-Myers Squibb and Sanofi-Aventis; A.S. reports having received unrestricted grant support for the Department of Cardiology from Bristol-Myers Squibb and Nycomed. The other authors report no potential conflicts of interest.

**References**


