Abciximab in primary coronary stenting of ST-elevation myocardial infarction: a European meta-analysis on individual patients’ data with long-term follow-up

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Aims Varying results have been reported in studies evaluating glycoprotein (GP) IIb/IIIa inhibition in primary coronary stenting of acute ST-elevation myocardial infarction (STEMI), usually with limited clinical follow-up. We performed a meta-analysis on case specific data of primary stenting in STEMI with a long-term evaluation.

Methods and results For this meta-analysis, studies of rescue percutaneous coronary intervention (PCI) after failed lytic therapy, plain balloon angioplasty studies and studies with an angiographic selection of patients were excluded. The ISAR-2, ADMIRAL, and ACE studies fulfilled inclusion criteria and all individual data were analysed together. The primary endpoint was the composite of death or re-infarction up to 3 years of follow-up. A total of 1101 patients, presenting for primary PCI and stenting of STEMI were randomized to abciximab (n = 550) or placebo (n = 551). This population had high-risk characteristics with 41% of anterior MI, 30% with a prior history of MI, 8.4% of cardiogenic shock, and 3.1% of previous coronary artery bypass graft (CABG). The primary endpoint of death or re-infarction was significantly reduced from an estimated cumulative hazard rate of 19.0% with placebo to 12.9% with abciximab [RR (95% IC): 0.633 (0.452; 0.887), \(P = 0.008\)]. The mortality rate was reduced from an estimated cumulative hazard rate of 14.3% in the placebo arm to 10.9% in the abciximab arm [0.695 (0.482; 1.003), \(P = 0.052\)]. Re-infarction was reduced from an estimated cumulative hazard rate of 5.5% with placebo to 2.3% with abciximab [0.41 (0.203; 0.831), \(P = 0.013\)]. Major bleedings were 2.5 and 2% with and without abciximab, respectively (NS). In the control arm, both the death or MI cumulative hazard rate (54 vs. 13.5%) and mortality rate (39.7 vs. 10.1%) were four-fold higher in diabetics when compared with non-diabetics. Abciximab provided a significant benefit on the primary endpoint for diabetics [0.525 (0.303; 0.911), \(P = 0.022\)].

Conclusion Abciximab has a strong and persistent impact on hard clinical endpoints in patients undergoing primary stenting for STEMI.

KEYWORDS
Primary percutaneous coronary intervention; Stent; GP IIb/IIIa Inhibitors; Abciximab; Myocardial infarction

Introduction
Glycoprotein (GP) IIb/IIIa inhibitors have been tested successfully in the prevention of coronary complications of elective percutaneous coronary intervention (PCI).1–5 Periprocedural myocardial infarction and the need for urgent repeat revascularization were reduced in these large studies, whereas early mortality rates were low and differences not statistically significant. Fewer and smaller randomized studies have also been conducted in primary PCI of ST-elevation myocardial infarction (STEMI) with or without stenting.6–10 Varying conclusions have been drawn from these trials and can be explained by differences in study design and populations selected. Moreover, none of these studies could examine hard outcomes (death or MI) and scarce information is available beyond 1 year of follow-up. Therefore, we decided to perform the first meta-analysis on case specific data of the stent trials performed with a comparable study design to provide information on hard outcomes at long-term follow-up.

Methods
Study objectives, design, and selected trials
Our primary aim was to compare, in STEMI treated by primary PCI and stenting, the effect of a concomitant administration of a GP IIb/IIIa inhibitor. We restricted our meta-analysis to trials that met all of the following criteria: (i) STEMI defined clinically

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without angiographic selection criteria; (ii) reperfusion therapy without fibrinolytic agent and with systematic primary stenting; (iii) primary hypothesis being a randomized comparison between a GP IIb/IIIa inhibitor or no GP IIb/IIIa inhibitor; (iv) record data on irreversible endpoints of death and re-infarction, with at least 1 year of follow-up; (v) principal investigators accepting to share all case specific data. The ISAR-2, ADMIRAL and ACE studies fulfilled these selection criteria. A Medline database (National Library of Medicine, Bethesda, Md) and Cochrane database search of the literature, scrutiny of the reference lists of trials and review articles, and meeting proceedings confirmed that there was no other randomized trial published in the last 10 years corresponding to these criteria. STEMI was defined according to the inclusion criteria of the trials concerned. Individuals patients’ data were requested on baseline entry characteristics, the allocated study treatment, dates of randomization, dates of last follow-up, and dates of outcomes events. Endpoints of interest were death, re-infarction, and major bleeding. Data were transferred in electronic format to the coordinating centre (Pitié-Salpêtrière University Hospital). For each study, extensive consistency and completeness checks were carried out, followed by preliminary analyses to ensure agreement with the main published results. Discrepancies were resolved by direct contact with the principal investigators.

Trial characteristics, endpoints, and definitions

The trial names, acronyms, main characteristics, and details of the study groups are shown in Table 1. Enrollment criteria of chest pain (<6 or <12 h) with ST-elevation on the ECG were used throughout but ISAR-2 had a wider definition and enrolled also patients presenting late (see Table 1). Trial design was broadly similar in all studies. All trials were randomized and controlled and one was double-blind with a placebo arm. There were minor differences regarding time and site of randomization: in one study randomization was possible at the scene of presentation or in the emergency room of the hospital, the drug being given during transportation to the catheterization laboratory. In all three studies, the GP IIb/IIIa inhibitor used was abciximab in the same dose regimen (a 0.25 mg/kg bolus followed by a 0.125 μg/kg/min infusion, to a maximum of 10 μg/min, over 12 h). All patients amenable to intracoronary stent placement received at least one stent. Only bare stents were used in these studies. The recommended stent was the Saint-Côme stent (Saint-Côme chirurgie, Marseilles, France) in ADMIRAL, the Carbolest (Sorin, Saluggia, Italy), and there was no recommended stent in ISAR-2. Initial event rates at 30 days were comparable in the control arms of the three studies as well as in the treated arms (Table 1).

The primary objective was the composite of death or re-infarction. We also examined, death, re-infarction and major bleedings as individual components up to 3 years of follow-up. Mortality was defined as death from any cause. Re-infarction was defined according to the definitions of the trials concerned. In the ACE and ADMIRAL studies, re-infarction was defined as recurrent chest pain with ST-segment or T-wave changes and recurrent elevation of cardiac enzymes. Diagnosis of re-infarction in ISAR-2 was based on typical chest pain, new ST-segment changes, and an increase in creatine kinase of at least 50% over the previous trough level in at least two samples reaching ≥240 U/L. Only one of the three studies had a follow-up longer than 3 years, then to limit statistical heterogeneity and lack of power beyond 3 years, maximum follow-up of this pooled analysis was censored at 3 years. Thus, 3-year follow-up was available in the ISAR-2 and ADMIRAL studies and 1-year follow-up was available in the ACE study. The sponsors of the individual studies had no role in the present study design, data collection, data analysis, data interpretation, and writing of the report, and no funding was obtained from any of these sponsors.

Table 1 Summary of characteristics in the three trials evaluating GPIIb/IIIa inhibition in primary stenting of AMI

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of publication</th>
<th>AMI % (n)</th>
<th>Previous AMI % (n)</th>
<th>CABG % (n)</th>
<th>Diabetics % (n)</th>
<th>Shock % (n)</th>
<th>GP IIb/IIIa</th>
<th>Study drug</th>
<th>Heparin dose (per procedure)</th>
<th>Death/AMI urgent revascularization at 30 days % (n)</th>
<th>GP IIb/IIIa inhibitor use</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-2</td>
<td>2000</td>
<td>4.2 (17)</td>
<td>210</td>
<td>0.4 (162)</td>
<td>40.4 (66)</td>
<td>14.9 (66)</td>
<td>70 IU/kg</td>
<td>abciximab</td>
<td>10,000 IU</td>
<td>5 (10)</td>
<td>abciximab</td>
</tr>
<tr>
<td>ADMIRAL</td>
<td>2001</td>
<td>2.5 (7)</td>
<td>151</td>
<td>2.5 (10)</td>
<td>38.7 (116)</td>
<td>8.3 (53)</td>
<td>Ticlopidin</td>
<td>abciximab</td>
<td>15,000 IU</td>
<td>6 (9)</td>
<td>Ticlopidin</td>
</tr>
<tr>
<td>ACE</td>
<td>2003</td>
<td>3.1 (5)</td>
<td>200</td>
<td>2.5 (10)</td>
<td>43.0 (173)</td>
<td>9.3 (37)</td>
<td>Ticlopidin</td>
<td>abciximab</td>
<td>70 IU/kg</td>
<td>4 (9)</td>
<td>Ticlopidin</td>
</tr>
</tbody>
</table>

et al.
Statistical analysis

Analyses of all randomized patients (intention-to-treat) are presented. Patient clinical data and duration of follow-up were available on an individual patient basis. The Kaplan–Meier method was used for estimation of the probability of event in each treatment group through the entire duration of follow-up and estimation of cumulative hazard rate. Meta-analysis has been carried out using a frailty model for Cox regression analysis (i.e. stratified Cox model, fixed treatment with a random treatment x study interaction)\(^{14}\) (R software version 1.7.1 was used for this calculation). In addition, robustness of the results have been checked using fixed effect models stratified on studies using SAS software version 9.1.3.\(^ {14}\)

Finally, the number of patients needed to be treated (NNT) during 3 years to avoid one event and its confidence intervals were calculated for each endpoint with a significant difference between the two groups using the methods proposed by Altman\(^ {15}\) [NNT = 1/(difference in estimated survival rates (over 3 years))].

As regards with bleedings, since the time of the event was not available and the number of events was low, a Fisher's test of available and the number of events was low, a Fisher's test of

\[ P = 0.052, \text{ no significant interaction was found, Figure 2A} \]

Clinical outcomes

Total number of death or re-infarction (primary outcome) observed among the 3 studies was 59 in the abciximab arm vs. 90 in the placebo arm. The estimated cumulative hazard rate for death or re-infarction was dramatically reduced to 12.9% in the abciximab arm vs. 19.0% in the placebo arm [RR (95% CI): 0.633 (0.452; 0.887), \( P = 0.008 \), no significant study by treatment interaction was found, Figure 1A]. The overall estimated NNT was 19 (11–135) for the primary clinical endpoint of this meta-analysis. Individual study results (hazard ratio and confidence intervals) and overall results of the meta-analysis are presented in Figure 1B. In the individual studies, 1 year cumulative hazard rates for death or re-infarction in placebo or abciximab groups were 20.5 vs. 6.7% in ACE, 10.5 vs. 8.8% in ISAR, and 17.3 vs. 12.1% in ADMIRAL. Total number of deaths were 49 vs. 69 among the three studies in the abciximab vs. placebo arms, respectively. Estimated cumulative hazard rate for death was 10.8% in the abciximab arm and 14.3% in the placebo arm and the difference was found at the limit of the significance level [0.695 (0.482; 1.003), \( P = 0.052 \), no significant interaction was found, Figure 2A and B], meaning a 3.5% absolute reduction and an overall NNT of 29 over the 3 years of follow-up. Interestingly, this benefit appeared early with curves diverging already in the first month of follow-up and remaining parallel beyond 1 year. Total number of re-infarction among the three studies was also reduced to 11 in the abciximab group vs. 26 in the placebo arm. Estimated cumulative hazard rate for re-infarction was significantly reduced in the abciximab group i.e. 2.25 vs. 5.5% in the placebo arm [RR 0.41 (0.203; 0.831), \( P = 0.013 \), no significant interaction was found] translating in a NNT of 31 (18–133). Among the three studies, major bleedings were observed in 14 patients in the abciximab arm vs. 11 patients in the placebo arm (\( P > 0.5 \)).

Among the pre-specified subgroups, shock patients and diabetic patients had the worst outcomes with estimated cumulative hazard rate for death in the control arm of 46.7 and 39.7%, respectively. At 3-year follow-up in the control arm, both the death or MI cumulative hazard rate (54 vs. 13.5%) and mortality rate (39.7 vs. 10.1%) were four-fold higher in diabetics than in non-diabetics. Abciximab provided a significant benefit on the primary endpoint for diabetics [0.525 (0.303; 0.911), \( P = 0.022 \), Figure 3A and B] with a NNT of 6 (4–64), while this effect remained at the limit of the significance level in non-diabetics [0.666 (0.439; 1.009), \( P = 0.055 \)]. The drug effect in diabetics was significant on re-infarction [0.153 (0.034; 0.69), \( P = 0.015 \)]; the impact on mortality, even if non-significant was important (abciximab decreased estimated cumulative hazard rate for death in diabetics from 39.7% to 28.6%) but comparable in diabetics and non-diabetics [0.654 (0.367; 1.163) and 0.677 (0.420; 1.092), respectively]. Similar results were found in patients with hypertension who had a significant effect of abciximab on the prevention of re-infarction [0.210 (0.06; 0.738), \( P = 0.015 \) and death or re-infarction [0.562 (0.358; 0.882), \( P = 0.012 \)], whereas the mortality effect of abciximab was comparable in patients with or without hypertension [0.672 (0.416; 1.087) and 0.744 (0.420; 1.316), respectively]. The other subgroups did not differ from the global population for the drug effect.

Results

Patient characteristics

A total of 1101 patients, more than 18 years old, presenting for primary PCI and stenting of STEMI were randomized to abciximab (\( n = 550 \)) or placebo (\( n = 551 \)). Exclusion criteria were bleeding diathesis, administration of thrombolytic agents for the current episode, neoplasm, recent stroke, uncontrolled hypertension, recent surgery, oral anticoagulant therapy, a limited life expectancy, childbearing potential, and known contraindications to therapy with aspirin, thienopyridines or heparin. Demographic characteristics, prior medical history, type of STEMI were well matched between the two groups as indicated in Table 2. This population had real life and moderate to high-risk characteristics with 41% of anterior acute myocardial infarction (AMI), 8.4% of cardiogenic shock, 3.1% of CABG and patients were not selected on the coronary status. All the patients received aspirin and unfractionated heparin as well as a thienopyridine after stenting.

Median follow-up duration was 365 days for the ACE study and 1095 days for the ISAR and ADMIRAL studies.

![Table 2. Baseline characteristics](https://academic.oup.com/hp/article-abstract/28/4/443/2887416/8648287/447)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Baseline characteristics</th>
<th>Placebo (( n = 551 ))</th>
<th>Abciximab (( n = 550 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male), % (n/N)</td>
<td>79.9 (440/551)</td>
<td>76.0 (417/549)</td>
<td></td>
</tr>
<tr>
<td>Age (years), Mean ( \pm SD )</td>
<td>61.3 ± 13</td>
<td>62.7 ± 12</td>
<td></td>
</tr>
<tr>
<td>Smoker, % (n/N)</td>
<td>43.1 (236/547)</td>
<td>41.0 (224/547)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, % (n/N)</td>
<td>49.1 (270/550)</td>
<td>51.9 (285/549)</td>
<td></td>
</tr>
<tr>
<td>Diabetes, % (n/N)</td>
<td>15.6 (86/550)</td>
<td>17.7 (97/549)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia, % (n/N)</td>
<td>39.6 (218/550)</td>
<td>41.5 (228/549)</td>
<td></td>
</tr>
<tr>
<td>Anterior AMI, % (n/N)</td>
<td>40.5 (223/551)</td>
<td>41.3 (227/550)</td>
<td></td>
</tr>
<tr>
<td>Cardiogenic shock, % (n/N)</td>
<td>9.1 (50/551)</td>
<td>7.8 (43/550)</td>
<td></td>
</tr>
<tr>
<td>Previous MI, % (n/N)</td>
<td>31.1 (171/550)</td>
<td>29.7 (163/548)</td>
<td></td>
</tr>
<tr>
<td>Previous CABG, % (n/N)</td>
<td>3.3 (18/551)</td>
<td>2.9 (16/550)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. (A) Death or re-infarction over 3 years of follow-up $P$-value = 0.008. (B) Death or re-infarction over 3 years of follow-up. Individual study results and meta-analysis results are presented with hazard ratio and 95% confidence intervals.

Figure 2. (A) Death of any cause over 3 years of follow-up $P$-value = 0.052. (B) Death of any cause over 3 years of follow-up. Individual study results and meta-analysis results are presented with hazard ratio and 95% confidence intervals.
The present study demonstrates a 37% relative risk reduction in death or re-infarction with abciximab in patients undergoing primary stenting for acute STEMI, a highly significant impact up to 3 years of follow-up. This risk reduction translates into 61 major events prevented for every 1000 patients treated, this benefit increasing five-fold in diabetics with 347 deaths or MI prevented for every 1000 diabetic patients treated. This drug effect on the primary endpoint is consistent with another major finding which is an overall 31% relative risk reduction of mortality in the global population over the same period, corresponding to 35 deaths avoided in a 1000 patients treated. In the field of reperfusion of STEMI, few medical interventions tested in the recent years can compare with this magnitude of benefit. The current demonstration of the impact of abciximab on long-term clinical outcomes including a strong reduction of mortality (although the $P$-value of 0.052 did not reach the statistical threshold of significance) in primary PCI confirms prior evidence from several trials, meta-analyses, and registries in coronary interventions scheduled in more stable patients.16–19 Several meta-analyses have also been published on mechanical reperfusion of STEMI, but in contrast to the present study all were performed on global data; moreover, most of them considered all studies available regardless of the study inclusion criteria leading to analyses of more heterogeneous populations including patients clinically or angiographically selected, patients treated with balloon only or with systematic stenting, and patients presenting for primary or rescue PCI.20–23 One of these studies suggested recently an effect of GP IIb/IIIa inhibition on mortality.23 Our study differs by the methodology used, the population studied, and the duration of follow-up: (i) the present methodology was based on a prospective protocol focusing on significant clinical trials and used updated data on individual patients from each trial keeping to a minimum any potential effect of reporting bias; this method differs from retrospective meta-analysis techniques on global and possibly incomplete data sets leading to potential biases inherent to the included studies; (ii) the present results have been obtained in a homogeneous study population representative of modern primary PCI practice; indeed, we excluded older balloon angioplasty studies, studies of rescue PCI following failure of thrombolysis, studies selecting MI patients on angiographic criteria, studies evaluating the combined use of GPIIb/IIIa inhibitors and lytics or studies without a comparison between active drug and control; (iii) finally, we also provide for the first time information on the impact of GPIIb/IIIa inhibition in STEMI beyond the usual 6–12 months follow-up.

The CADILLAC study (which did not meet two of the inclusion criteria of the present meta-analysis), in its comparison between abciximab and control, found statistically significant and clinically meaningful reductions in the
30-day composite endpoint of death, recurrent MI, and ischaemia-driven TVR (6.8 vs. 4.6%, \( P = 0.01 \)), like it had been observed separately in the three trials included in the present meta-analysis.\(^9\),\(^24\) However and conversely to the present results, such benefits with abciximab treatment were not observed in the subgroup of stented patients when the four treatment arms of the CADILLAC trial were compared in particular at 12 months follow-up. The CADILLAC study remains the largest trial in primary PCI of STEMI with a total of 1036 stented patients followed up for a year. The present study provides data of similar power with a total of 1101 stented patients and with a longer follow-up. The apparent discrepancies between the two studies may clearly relate to differences in trial design. Protocol-specified differences in the CADILLAC trial relating to angiographic selection of patients and exclusion of patients with cardiogenic shock or coronary bypass graft involvement imply lower risk population as shown by the death rate in the control arm at 1 year,\(^24\) which was three times lower than in the present meta-analysis. Moreover, the choice of a primary endpoint reflecting clinical restenosis in CADILLAC disproved the initial efficacy of abciximab on thrombotic events, which was offset by late TVR events.

Our data underscores the poor long-term prognosis of diabetic patients suffering a myocardial infarction with a 3-year mortality cumulative hazard rate of 39.7% and a death or MI rate of 54% over the same period, in the control arm. Only the subgroup of shock patients had more severe outcomes but in contrast to shock patients who had a high early mortality rate, the risk of diabetics gradually increased over time. Abciximab reduced significantly the primary endpoint of death or MI in diabetics by 47.5% (relative risk reduction) over the 3 years of follow-up with an impressive 85% relative risk reduction of re-MI. Although non-significant, the drug effect on death was present with an 11% absolute risk reduction over 3 years, a much larger benefit than the 2–3% absolute risk reductions seen in previous retrospective meta-analyses in diabetics undergoing scheduled PCI with short-term follow-up.\(^1\)\(^2\),\(^25\),\(^26\) However, it should be kept in mind that the diabetic population is relatively small inducing relatively large width for confidence intervals. Whether this long-term drug effect is related to the initial antiplatelet effect of abciximab or to anti-inflammatory or non-specific properties of the drug, cannot be determined by our study. Although hypertensive patients had a much better prognosis than diabetic patients, a similar drug effect was observed.

Only a subset of the ADMIRAL population, representing less than 7% of the population of this meta-analysis, received the drug early in the ER or in the ambulance. Pre-catheterization laboratory initiation of therapy has been associated with a 28% reduction of mortality compared with in-catheterization laboratory initiation of the drug in a meta-analysis of randomized studies using either tirofiban or abciximab in STEMI patients undergoing primary PCI.\(^27\) Another recent pooled analysis of six randomized or non-randomized studies performed with abciximab, found similarly a 42% reduction of death at 30 days with an early administration compared to a later start of the drug at the time of PCI.\(^28\) A systematic early use of GP IIb/IIIa inhibitors would amplify further the survival benefit seen in the present analysis. These recent studies outline that time is an issue not only for stent implantation but also for GP IIb/IIIa inhibition.

Our analysis also documented a moderate increase of major bleedings with abciximab (though unlike fibrinolytic therapy, intracranial hemorrhage was not increased). This 0.6% absolute excess of major bleedings must be put into perspective with the 3.6% absolute reduction of mortality or 5.6% absolute reduction of death or MI. Although favourable, this risk benefit ratio can be improved further by a more cautious dosing of heparin, a close attention to sheath management, or use of the transradial approach. The present work has potential limitations inherent to meta-analyses such as inevitable differences between trials, differences in definitions of MI, different lengths of follow-up, but despite these limitations, a significant improvement in hard clinical outcomes up to 3 years has been observed, suggesting that the results can be generalized to a broad patient population undergoing PCI with this GP IIb/IIIa inhibitor. Although new drugs or new strategies with antiplatelet therapy appear to refine the clinical application of GP IIb/IIIa inhibitors in coronary intervention, our findings confirm and clarify the early efficacy of abciximab therapy in mechanical reperfusion of STEMI for reducing serious ischaemic events, a clinical benefit which is maintained during longer term follow-up.

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Abciximab in primary coronary stenting of STEMI


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