Abciximab as Adjunctive Therapy to Reperfusion in Acute ST-Segment Elevation Myocardial Infarction: A Meta-analysis of Randomized Trials

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In Reply:
Abciximab as Adjunctive Therapy to Reperfusion in Acute ST-Segment Elevation Myocardial Infarction
A Meta-analysis of Randomized Trials

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The treatment of ST-segment elevation myocardial infarction (STEMI) has substantially evolved over the past decades, mainly due to the adoption of pharmacological and mechanical reperfusion therapies1,2 and improvement in antiplatelet and anticoagulation therapies.3-35 However, despite successful revascularization, suboptimal reperfusion may occur, resulting in unfavorable outcome.39 The strategy of adding glycoprotein (Gp) IIb/IIIa inhibitors to both pharmacological and mechanical reperfusion would appear attractive.

Several studies have shown that abciximab is associated with better tissue reperfusion and better recovery of left ventricular function.31-33 The underlying mechanisms for these beneficial effects may be diminished distal embolization of platelet aggregates or inhibition of direct interaction of platelets with the reperfused endothelium by abciximab.35,36 Particularly when combined with fibrinolysis, which has been shown to increase platelet activation during thrombolysis, abciximab is associated with better tissue reperfusion and better recovery of left ventricular function.37-39 The benefits of abciximab in patients with ST-segment elevation myocardial infarction (STEMI) are still a matter of debate.

Objective To combine data from all randomized trials conducted with abciximab in STEMI.

Data Sources Formal searches of electronic databases (MEDLINE, PubMed) from January 1990 to December 2004.

Study Selection We examined all completed, published, randomized trials of abciximab in STEMI. The following key words were used for study selection: randomized trial, myocardial infarction, reperfusion, primary angioplasty, facilitated angioplasty, stenting, fibrinolysis, Ilb-IIia inhibitors, and abciximab.

Data Extraction Information on study design, type and dosage of drugs, inclusion and exclusion criteria, number of patients, and clinical outcome was extracted by 2 investigators. Disagreements were resolved by consensus.

Data Synthesis Eleven trials were analyzed, involving 27115 patients (12 602 [46.5%] in the abciximab group, 14 513 [53.5%] in the control group). When compared with the control group, abciximab was associated with a significant reduction in short-term (30 days) mortality (2.4% vs 3.4%, P = .047) and long-term (6-12 months) mortality (4.4% vs 6.2%, P = .01) in patients undergoing primary angioplasty but not in those treated with fibrinolysis or in all trials combined. Abciximab was associated with a significant reduction in 30-day reinfarction, both in all trials combined (2.1% vs 3.3%, P < .001), in primary angioplasty (1.0% vs 1.9%, P = .03), and in fibrinolysis trials (2.3% vs 3.6%, P < .001). Abciximab did not result in an increased risk of intracranial bleeding (0.61% vs 0.62%, P = .62) but was associated with an increased risk of major bleeding complications when combined with fibrinolysis (5.2% vs 3.1%, P < .001) but not with primary angioplasty (4.7% vs 4.1%, P = .36).

Conclusions This meta-analysis shows that, when compared with the control group, adjunctive abciximab for STEMI is associated with a significant reduction in 30-day and long-term mortality in patients treated with primary angioplasty but not in those receiving fibrinolysis. The 30-day reinfarction rate is significantly reduced in patients treated with either fibrinolysis or primary angioplasty. A higher risk of major bleeding complications is observed with abciximab in association with fibrinolysis.
and aggregation. To reduce the risk of bleeding complications, half-dose fibrinolytic therapy has been proposed in combination with abciximab.

However, the effect of Gp IIb/IIIa inhibitors on outcomes in patients with STEMI remains controversial. Previous meta-analyses have been restricted to primary angioplasty trials and have failed to include all randomized trials. Since only a few small trials have been conducted on tirofiban and epifibatide, we performed a comprehensive meta-analysis of all randomized trials with abciximab as adjunctive therapy in treatment of STEMI.

METHODS
Eligibility and Search Strategy
We obtained results from all completed, published, randomized trials of abciximab in STEMI. The literature was scanned by formal searches of electronic databases (MEDLINE, PubMed) from January 1990 to December 2004, and the scientific session abstracts in Circulation—Journal of the American College of Cardiology, and European Heart Journal from January 1999 to December 2004. The following key words were used: randomized trial, myocardial infarction, reperfusion, primary angioplasty, facilitated angioplasty, stenting, fibrinolysis, IIb-IIIa inhibitors, and abciximab. The treatment and the control groups within each trial had to receive the same primary reperfusion treatment (fibrinolysis or primary angioplasty).

Data Extraction
Information on study design, type and dosage of drugs, inclusion and exclusion criteria, number of patients, and clinical outcome was extracted by 2 investigators. Disagreements were resolved by consensus. In case of incomplete or unclear data, authors were contacted where possible. Data were managed according to the intention-to-treat principle.

Outcomes
Primary end points were mortality at 30 days and at long-term follow-up. The secondary end point was reinfarction at 30 days. Safety end points included intracranial bleeding and other major bleeding complications (defined by Thrombolysis in Myocardial Infarction [TIMI] or Global Utilization of Strategies to Open Occluded Arteries [GUSTO] criteria).

Data Analysis
Statistical analysis was performed using Review Manager 4.27 (The Cochrane Collaboration, Oxford, England), SPSS 11.5 (SPSS Inc, Chicago, Ill), and SAS version 8.2 (SAS Institute Inc, Cary, NC). Odds ratios (ORs) and 95% confidence intervals (CIs) were used as summary statistics. The pooled OR was calculated by using a fixed-effects model with the Mantel-Haenszel method, and the Breslow-Day test was used to examine the statistical evidence of heterogeneity across the studies (P < .10). The DerSimonian and Laird random-effects model was additionally applied to calculate pooled ORs in case of significant heterogeneity across studies. A first analysis was conducted including all trials. Prespecified subanalyses were performed according to the treatment of interest (fibrinolysis or primary angioplasty).

The potential publication bias was examined by constructing a funnel plot in which sample size was plotted against ORs for the primary end point available from all studies. In addition, a linear regression approach to measure funnel plot asymmetry was used. The influence of individual studies on the summary effect estimates was evaluated by reestimating and plotting the summary OR in the absence of each study.

According to absolute risk reduction or increment, we calculated the number needed to treat to prevent 1 event, whereas for the safety end points we calculated the number needed to harm to determine 1 adverse event.

RESULTS
A total of 13 randomized trials were identified. One study was part of the ISAR trial and so was excluded from analysis; another study was also excluded because complete follow-up data were not available. Therefore, a total of 11 trials were analyzed (Table), involving 27115 patients (12,602 [46.5%] in the abciximab group, 14,513 [53.5%] in the control group). Eight trials including 3949 patients were conducted in primary angioplasty, whereas 3 trials conducted with fibrinolysis included 23,166 patients (85.3% of the entire meta-analysis). In all trials except for ASSENT-3 and ENTIRE-TIMI 23, weight-adjusted unfractioned heparin was used (Table). In all patients from fibrinolysis trials, full-dose abciximab was given in association with half-dose fibrinolytic therapy. In the study by Petrov et al, mechanical revascularization was performed after failed fibrinolysis.

Primary End Points
Mortality at 30 Days. As shown in Figure 1, abciximab was not associated with a significant reduction in 30-day mortality in all trials combined (5.2% vs 5.9%; OR, 0.97; 95% CI, 0.87-1.08; P = .61 [P = .38 for heterogeneity; P = .08 for heterogeneity between reperfusion strategies]) or in fibrinolysis trials (5.8% vs 5.8%; OR, 1.0; 95% CI, 0.9-1.12; P = .95 [P = .25 for heterogeneity]). A significant reduction in mortality was observed only in angioplasty trials (2.4% vs 3.4%; OR, 0.68; 95% CI, 0.47-0.99; P = .047 [P = .77 for heterogeneity]). According to a risk reduction of 1.0% in primary angioplasty trials, we estimated a number needed to treat of 100 to prevent 1 death at 30-day follow-up.

Long-term Mortality. As shown in Figure 2, abciximab was not associated with a significant reduction in long-term (6-12 months) mortality in the overall cohort of patients (7.9% vs 8.0%; fixed-effects model: OR, 1.00; 95% CI, 0.91-1.09; P = .98; random-effects model: OR, 0.88; 95% CI, 0.71-1.09; P = .25 [P = .03 for heterogeneity; P = .01 for heterogeneity between reperfusion strategies]) or in fibrinolysis trials (8.6% vs 8.3%; OR, 1.04; 95% CI, 0.95-1.15; P = .41 [P = .15 for heterogeneity]). Significant benefits were observed in pri-
primary angioplasty trials (4.4% vs 6.2%; OR, 0.69; 95% CI, 0.52-0.92; P = .01 [P = .15 for heterogeneity]). According to a risk reduction of 1.8% in primary angioplasty trials, we estimated a number needed to treat of 55.6 to prevent 1 death at long-term follow-up.

Secondary End Points

Reinfarction at 30 Days. As shown in Figure 3, abciximab was associated with a reduction in 30-day reinfarction in all trials combined (2.1% vs 3.3%; OR, 0.63; 95% CI, 0.54-0.73; P < .001 [P = .66 for heterogeneity; P = .56 for heterogeneity between reperfusion strategies]), in primary angioplasty trials (1.0% vs 1.9%; OR, 0.56; 95% CI, 0.33-0.94; P = .03 [P = .51 for heterogeneity]), and in fibrinolysis trials (2.3% vs 3.6%; OR, 0.64; 95% CI, 0.54-0.75; P < .001 [P = .48 for heterogeneity]).

According to the absolute risk reduction, we estimated a number needed to treat of 83.3 in all trials combined, 111.1 in primary angioplasty trials, and 76.9 in fibrinolysis trials, to prevent 1 reinfarction at 30 days.

Safety End Point. Abciximab was not associated with a higher incidence of intracranial bleeding in all studies combined (0.61% vs 0.62%; OR, 1.08; 95% CI, 0.79-1.46; P = .62 [P = .93 for heterogeneity; P = .95 for heterogeneity between reperfusion strategies]), in angioplasty trials (0.06% vs 0.11%; OR, 0.97; 95% CI, 0.31-3.01; P = .96 [P = .93 for heterogeneity]), or in fibrinolysis trials (0.70% vs 0.69%; OR, 1.09; 95% CI, 0.79-1.49; P = .60 [P = .44 for heterogeneity]). However, abciximab was associated with a higher incidence of bleeding complications in all trials (5.2% vs 3.2%; fixed-effects model: OR, 1.66; 95% CI, 1.47-1.88; P < .001; random-effects model: OR, 1.51; 95% CI, 1.15-1.98; P < .001 [P = .02 for heterogeneity and for heterogeneity between reperfusion strategies]) and in fibrinolysis trials (5.2% vs 3.1%; OR, 1.77; 95% CI, 1.35-2.03; P < .001 [P = .13 for heterogeneity]), with a number needed to harm of 50 and 47.6, respectively, whereas no difference was observed in angioplasty trials (4.7% vs 4.1%; OR, 1.16; 95% CI, 0.85-1.59; P = .36 [P = .12 for heterogeneity]).

### Assessment of Publication Bias

The potential publication bias for the primary end point (mortality at 30 days) was assessed using funnel plots with Begg and Mazumdar test and Egger's test. All studies were included in these analyses. As shown in Figure 4, there were no outliers and the number of studies was sufficient for each treatment group. The phenomenon of publication bias, defined as the difference in primary and secondary outcomes, was not detected. The funnel plots were symmetric, and this suggests that there is no publication bias. A publication bias was not observed in any of the studies, and the funnel plot is symmetric with a random distribution of studies. The number of studies was sufficient for each treatment group for the assessment of publication bias. The funnel plots are symmetric, and this suggests that there is no publication bias. The phenomenon of publication bias, defined as the difference in primary and secondary outcomes, was not detected.
was analyzed by the visual analysis of the funnel plot (Figure 4) and by the mathematical estimate of the asymmetry of this plot provided by a linear regression approach. The intercept of the regression line did not deviate significantly from zero ($\alpha = -0.1$; 95% CI, $-0.28$ to $0.08$; $P = .40$). Individual studies did not influence the effect estimates of the meta-analysis.

**COMMENT**

The aim of the current study was to perform a comprehensive, updated meta-analysis of all randomized trials with abciximab as adjunctive therapy in management of STEMI. Previous meta-analyses have been restricted to primary angioplasty trials and have failed to include all currently available randomized trials.38-41

The main finding of this meta-analysis is that adjunctive abciximab therapy is associated with a significant reduction in 30-day reinfarction in patients with STEMI treated with either pharmacological or mechanical reperfusion, whereas a significant reduction in short- and long-term mortality was observed only in patients undergoing primary angioplasty. Abciximab was not associated with an increased risk of intracranial bleeding, whereas a higher risk of major bleeding complications was observed in conjunction with fibrinolytic therapy. However, the GUSTO V and ASSENT-3 trials have shown that abciximab in conjunction with fibrinolysis is associated with an increased risk of intracranial bleeding in elderly patients.

The benefits in mortality with abciximab in patients treated with primary angioplasty may be related to the fact that abciximab may prevent distal embolization and improve myocardial perfusion. As reported by Henriques et al,46 distal embolization is observed in up to 16% of patients undergoing primary angioplasty, resulting in impaired myocardial perfusion and high long-term mortality.

Given the advances in fibrinolysis and primary angioplasty of the last decades,1,2 further attempts to reduce mortality are not easily demonstrated. Highly selected non–high-risk patients are commonly enrolled in randomized trials, whereas benefits on mortality have been shown in trials enrolling only high-risk patients.3,10,14,16,18 Several nonrandomized studies have shown significantly bet-
ter survival in patients with cardiogenic shock treated with primary angioplasty and abciximab.

Still a matter of debate is the timing of administration of abciximab. Although primary angioplasty has been shown to be superior to fibrinolysis, the time delay related to transportation to tertiary centers remains a major drawback, particularly in high-risk patients. In most trials, abciximab was administered just before the angioplasty procedure. Among angioplasty trials, only in the ADMIRAL trial was abciximab started earlier in all patients. This resulted in improvement of preprocedural angiographic flow and subsequent clinical outcome, particularly when therapy was started in the ambulance or emergency department. However, randomized trials conducted so far have shown no benefits from pretreatment with fibrinolysis in patients undergoing primary angioplasty. This may be due to the potential platelet aggregation induced by fibrinolysis. Furthermore, since the role of Gp IIb/IIIa inhibitors is to protect the microcirculation from platelet aggregation and leukocyte plugging, intracoronary administration of Gp IIb/IIIa inhibitors might be more effective than intravenous administration at the time of balloon inflation. In addition, the effect of abciximab on mortality in diabetic patients with STEMI is still unclear. Only in the GUSTO V, ASSENT-3, and ADMIRAL trials were subanalyses conducted in diabetic patients, and these results were conflicting.

There are several limitations to this study. Our meta-analysis was not performed on individual patient data, because complete individual data were not available from all studies. Moreover, a larger proportion of patients included in this meta-analysis have been enrolled in fibrinolysis trials. Even though patients in the study by Petronio et al were randomized after failed fibrinolysis, this study was included in the angioplasty group because this trial was conducted to evaluate the additional benefits of abciximab in patients undergoing planned mechanical revascularization. Furthermore, subanalysis was not performed in patients undergoing primary stenting or balloon angioplasty. However, recent data from large randomized trials have shown that primary stenting, with or without abciximab, has no additional benefits in terms of death and reinfarction, which are the only end points of this meta-analysis.

Although the very low rate of intracranial bleeding (observed in only 1 patient [0.06%]) in primary angioplasty trials would suggest the safety of abciximab, more information on the interaction between age and the risk of intracranial bleeding should be reported in future randomized trials.

This meta-analysis was not able to evaluate the benefits of abciximab according to all potential strategies (primary angioplasty, fibrinolysis, or fibrinolysis followed by angioplasty). In almost all fibrinolysis trials, angioplasty was performed as rescue therapy in case of failed fibrinolysis, whereas only 1 study focused on angioplasty after fibrinolysis. Furthermore, both visual and mathematical analysis cannot completely exclude any publication bias. Finally, the conclusions of this meta-analysis cannot be extended to other Gp IIb/IIIa inhibitors such as tirofiban and eptifibatide.

This meta-analysis shows that abciximab, as adjunctive therapy to both primary angioplasty and fibrinolytic

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therapy for STEMI, is associated with a significant reduction in short-term reinfarction rate, whereas the benefits in reducing mortality are observed only in association with primary angioplasty. Abciximab is not associated with an increased risk of intracranial hemorrhage (except in combination with fibrinolysis in elderly patients), whereas a higher risk of major bleeding complications is observed only in association with fibrinolysis.

Until the results of large randomized trials are available, this meta-analysis suggests that abciximab should be strongly considered in primary angioplasty for STEMI, particularly in high-risk patients, whereas the combination of abciximab and fibrinolysis should be avoided due to the observed higher risk of bleeding complications, particularly in elderly patients.

Author Contributions: Dr De Luca had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: De Luca, Suryapranata, Stone, Antoniucci, Antman, Topol.

Acquisition of data: De Luca, Suryapranata, Antman.

Analysis and interpretation of data: De Luca, Suryapranata, Stone, Antoniucci, Tcheng, Neumann, Van der Wef.

Drafting of the manuscript; statistical analysis: De Luca, Topol.

Critical revision of the manuscript for important intellectual content; study supervision: Suryapranata, Stone, Antoniucci, Tcheng, Neumann, Van der Wef, Antman.

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REFERENCES


... and then the day came when the risk to remain tight in a bud was more painful than the risk it took to blossom.
—Anais Nin (1903-1977)