Effect of Abciximab on Prothrombin Activation and Thrombin Generation in Acute Coronary Syndromes Without ST-Segment Elevation

Global Utilization of Strategies to Open Occluded Coronary Arteries Trial IV in Acute Coronary Syndromes (GUSTO IV ACS) Italian Hematologic Substudy

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Background—Abciximab is very effective in reducing major cardiac events in patients undergoing interventional procedures. Its antithrombotic effect is primarily attributable to the blocking of platelet glycoprotein IIb/IIIa receptors, but recent evidence suggests that it may have a direct antithrombin effect. No data are available concerning the effect of abciximab on the in vivo markers of prothrombin activation and thrombin generation in patients with acute coronary syndromes without ST elevation.

Methods and Results—We measured the plasma levels of prothrombin fragment 1+2 (a marker of prothrombin activation) and the thrombin/antithrombin complex (a marker of thrombin generation) in 167 patients with acute coronary syndromes without ST elevation enrolled in the GUSTO IV ACS trial who were randomized to receive abciximab for 24 hours (52 patients), abciximab for 48 hours (59 patients), or placebo (56 patients) in addition to heparin. Blood samples were obtained at baseline (before any treatment), after 24 and 48 hours (before study drug discontinuation), and 1 month later. There was a significant increase in the plasma levels of prothrombin fragment 1+2 after 48 hours and after 1 month in all 3 groups, placebo (P=0.0001), 24-hour abciximab (P=0.0002), and 48-hour abciximab (P=0.0001). The plasma thrombin/antithrombin complex levels were similar in the 3 groups at all time points and did not change during the study drug infusions.

Conclusions—Abciximab does not decrease prothrombin activation and thrombin generation in patients with acute coronary syndromes without ST elevation not undergoing interventional procedures. (Circulation. 2002;105:928-932.)

Key Words: coronary disease ■ glycoproteins ■ inhibitors ■ thrombin

Antithrombotic therapy with heparin and aspirin is the standard treatment in patients with acute coronary syndromes without ST-segment elevation.1,2 However, despite the relative benefit of this standard therapy, most recent trials show that 5% to 20% of patients still experience death or myocardial infarction during the 30 days after initial hospitalization.3 Aspirin is a relatively weak inhibitor of platelet aggregation, and its blockade of the cyclooxygenase pathway can be overcome by the activation of other agonist pathways, including thrombin, collagen, and epinephrine. Heparin is effective in reducing thrombin activity and thrombin potential in vitro,4-7 but it cannot inhibit prothrombin activation in vivo as expressed by prothrombin fragment 1+2 (F1+2).8 Recent evidence suggests that the coagulation activation detected by increased in vivo F1+2 determinations is associated with an increased risk of cardiac events in patients with acute coronary syndromes.9,10 Platelet activation by all agonists can be blocked by glycoprotein IIb/IIIa (GPIIb/IIIa) receptor antagonists. The results of recent trials suggest that, when added to heparin and aspirin, short-term intravenous GPIIb/IIIa antagonist treat-
ment can decrease the incidence of ischemic cardiac events in patients with acute coronary syndromes without ST-segment elevation during hospitalization and after 30 days.11–13

Platelet adhesion is the first event in the coagulation process and is immediately followed by the release of mediators and the activation/externalization of GPIIb/IIIa receptors, which are responsible for platelet aggregation and additional recruitment as a result of fibrinogen binding. After activation, phospholipoproteins are available on the platelet surface for the catalytic activation of the tenase and prothrombinase complexes that are actually responsible for the generation and activation of thrombin. Blocking GPIIb/IIIa receptors by interfering with such a crucial initial amplifying process may be critical for inhibiting additional reactions in the coagulation cascade. The aim of this study was to assess the effects of prolonged abciximab infusion on thrombin generation in patients with acute coronary syndromes without ST-segment elevation not undergoing interventional procedures.

Methods

Patient Population

The Italian Hematologic Substudy involved all of the patients enrolled in the GUSTO IV ACS trial at the Department of Cardiology IRCCS Policlinico San Matteo, Pavia; Division of Cardiology, Ospedale di Bentivoglio, Bentivoglio; Division of Cardiology, Ospedale Civile, Caserta; Division of Cardiology, Azienda Ospedaliera “Maggiore della Carità,” Novara; Cardiovascular Department, General Hospital, Treviso; Division of Cardiology, Ospedale Agnelli, Pinerolo; Division of Cardiology, Centro Cardiologico Monzino, Milan; Division of Cardiology, Ospedale S. Antonio Abate, Gallarate; and Division of Cardiology, Ospedale Niguarda, Milan, Italy.

The GUSTO IV ACS study enrolled patients with symptoms of cardiac ischemia at rest lasting >5 minutes if they had either a positive cardiac troponin T or I test (above the upper normal limit for the local qualitative or quantitative assay) or a previously unknown elevation during hospitalization and after 30 days.11 The specific exclusion criteria for the Italian Hematologic Substudy were comorbid conditions known to alter coagulation system function, such as age >70 years, active peptic ulcer disease, a history of stroke, oral anticoagulation within the previous 7 days, a platelet count <100,000/μL, confirmed hypertension, a history of vasculitis, or a punctured noncompressible vessel within the 24 hours preceding enrollment.

The specific exclusion criteria for the Italian Hematologic Substudy were comorbid conditions known to alter coagulation system function, such as age >70 years, active peptic ulcer disease, a history of stroke, oral anticoagulation within the previous 7 days, a platelet count <100,000/μL, confirmed hypertension, a history of vasculitis, or a punctured noncompressible vessel within the 24 hours preceding enrollment.

The study approved by the Institutional Review Board of the Ca’ Granda Niguarda Hospital (Milan, Italy), and written informed consent was obtained from all of the patients.

Blood Sampling and Biochemical Determinations

Venipunctures were performed atraumatically by means of 19-gauge butterfly infusion sets. The first 8 mL of blood was used for other biochemical determinations. The samples for the thrombin/antithrombin complex (TAT) and prothrombin F1+2 assays were collected directly into vacutainers containing sodium citrate at a final concentration of 3.8% (wt/vol). All of the blood samples were immediately centrifuged at 2500g for 25 minutes at 4°C, and the plasma was frozen at −80°C until analysis.

All of the samples were analyzed without any knowledge of the clinical data. F1+2 was measured using a commercially available enzyme-linked immunosorbent assay (Enzygnost F12; Behringwerke AG). Because the calibration curve was linear only up to 2 mmol/L, the samples with F1+2 levels of >2 mmol/L were diluted with PBS (phosphate, 0.04 mol/L and saline, 0.1 mol/L; pH 7.4) to obtain absorbance within the linear part of the calibration curve. This technique has an intra-assay coefficient of variation of 5% and an upper normal limit of 2.3 mmol/L.

The plasma concentration of thrombin/antithrombin was measured using a commercially available kit (Enzygnost TAT, Behringwerke AG). The coefficient of variation of this method is 5%, and the upper normal limit is 4.9 ng/L.

Statistical Analysis

The descriptive statistics include mean values and standard deviations or median and 25th and 75th percentiles, as appropriate. Baseline characteristics were compared using ANOVA for continuous data and the χ2 test for categorical data. Given that the plasma levels of F1+2 and TAT were not normally distributed, Kruskall–Wallis’ 1-way ANOVA was used to test the differences between groups; subsequent comparisons were made using the Mann–Whitney U test. Repeated measures were compared by means of Friedman’s test, and subsequent pairwise comparisons with baseline were made using Wilcoxon’s signed-rank test. All of the tests were 2-tailed, and P<0.05 was regarded as statistically significant.

Results

Patient Characteristics

The study involved 167 consecutive patients: 56 randomized to placebo, 52 to 24-hour abciximab infusion, and 59 to 48-hour abciximab infusion. Their demographic and clinical characteristics are shown in Table 1.

On the basis of central determinations, 63 patients (37%) had a negative troponin T test (<0.1 mg/L) and 98 patients (58%) had a positive test; it was not determined in 6 patients (4%). Thirty-one of the patients randomized to placebo (48%), 24 randomized to 24-hour abciximab infusion (50%), and 29 randomized to 48-hour abciximab infusion (52%) were receiving heparin before randomization (P=NS). The mean activated partial thromboplastin time was similar in the 3 groups before the start of treatment (Table 2) and signifi-
TABLE 1. Demographic and Clinical Characteristics of the Study Population (n=167 Patients)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n=56)</th>
<th>24-h Abciximab (n=52)</th>
<th>48-h Abciximab (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean</td>
<td>66.5±11.9 (44–87)</td>
<td>66.1±12 (22–89)</td>
<td>63.1±11.2 (39–83)</td>
</tr>
<tr>
<td>Male sex</td>
<td>36 (64%)</td>
<td>36 (69%)</td>
<td>41 (69%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (61%)</td>
<td>33 (64%)</td>
<td>36 (61%)</td>
</tr>
<tr>
<td>Smokers</td>
<td>30 (53%)</td>
<td>29 (56%)</td>
<td>31 (52%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (23%)</td>
<td>13 (25%)</td>
<td>14 (21%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>16 (28%)</td>
<td>23 (37%)</td>
<td>23 (39%)</td>
</tr>
<tr>
<td>Time from index event, h</td>
<td>9.7±6.46 (2–22)</td>
<td>10.2±6.6 (2–24)</td>
<td>11.8±6.2 (1.5–24)</td>
</tr>
<tr>
<td>Mean duration of study drug infusion, h</td>
<td>47.3±5.4</td>
<td>47.1±7.7</td>
<td>47.1±4.1</td>
</tr>
</tbody>
</table>

Values are mean±SD (range) or n (%).

The median and 25th and 75th percentiles of the plasma F1\(2\) levels at the different time points in the patients receiving 24-hour abciximab infusion are shown in Table 3. There was no significant difference after 24 hours (median change, 0.1 nmol/L; −0.3 to 0.4), whereas there was a significant increase of 0.35 nmol/L (0 to 0.9) after 48 hours (\(P=0.003\)). After 1 month, the median increase in plasma F1\(2\) levels was 0.45 nmol/L (0.02 to 0.95) compared with baseline (\(P=0.0001\)).

The median and 25th and 75th percentiles of the plasma TAT levels at the different time points are shown in Table 4. There was no significant difference in TAT plasma levels during the 24-hour study drug infusion period (median change, −0.3 ng/mL; −1.4 to 4.5) and no change 24 hours after study drug discontinuation (median change, 0 ng/mL; −0.1 to 5.9). After 1 month, the levels were similar to those found at baseline, with a median change of 0.2 ng/mL (−0.77 to 1.5).

TABLE 2. Median Activated Partial Thromboplastin Time (25th to 75th Percentiles) in the 3 Treatment Groups at Different Time Points

<table>
<thead>
<tr>
<th>Time Points</th>
<th>Placebo (n=56)</th>
<th>24-h Abciximab (n=52)</th>
<th>48-h Abciximab (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline aPTT</td>
<td>38 (28–67)</td>
<td>31 (27–47)</td>
<td>31 (27–53)</td>
</tr>
<tr>
<td>24-h aPTT</td>
<td>51 (46–65)</td>
<td>54 (43–65)</td>
<td>50 (41–67)</td>
</tr>
<tr>
<td>48-h aPTT</td>
<td>53 (45–64)</td>
<td>50 (40–60)</td>
<td>53 (43–60)</td>
</tr>
</tbody>
</table>

aPTT indicates activated partial thromboplastin time.

Forty-Eight-Hour Abciximab Treatment Group

The median and 25th and 75th percentiles of the plasma F1\(2\) levels at the different time points in the patients receiving 48-hour abciximab infusion are shown in Table 3. There was no significant difference during the first 24-hour treatment period (median change of 0.15 nmol/L; −0.15 to 0.67), whereas there was a significant increase of 0.3 nmol/L (−0.35 to 1.1) at the 48-hour evaluation (\(P=0.004\)). After 1 month, the plasma F1\(2\) levels had increased by 0.3 nmol/L (−0.17 to 0.8) compared with baseline (\(P=0.01\)).

TABLE 3. Median Prothrombin Fragment 1+2 Levels (25th to 75th Percentiles) in the 3 Treatment Groups

<table>
<thead>
<tr>
<th>Time Points</th>
<th>Placebo (n=56)</th>
<th>24-h Abciximab (n=52)</th>
<th>48-h Abciximab (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline F1+2</td>
<td>1.05 (0.7–1.7)</td>
<td>1.1 (0.8–1.7)</td>
<td>1.1 (0.8–1.8)</td>
</tr>
<tr>
<td>24-h F1+2</td>
<td>1.1 (0.9–1.8)</td>
<td>1.1 (1.0–1.6)</td>
<td>1.2 (0.8–1.8)</td>
</tr>
<tr>
<td>48-h F1+2</td>
<td>1.5 (1.1–2.0)*</td>
<td>1.6 (1.1–2.4)†</td>
<td>1.5 (1.0–2.6)‡</td>
</tr>
<tr>
<td>1-mo F1+2</td>
<td>1.6 (1.1–2.5)*</td>
<td>1.6 (1.2–2.3)*</td>
<td>1.6 (1.2–2.3)§</td>
</tr>
</tbody>
</table>

\(P\) 0.0001 0.002 0.0001

\(\ast P=0.0001\) vs baseline; \(\dagger P=0.003\) vs baseline; \(\ddagger P=0.004\) vs baseline; and \(\S P=0.01\) vs baseline.
platelets also release activated factor V from their granules, which coagulation reactions occur. In addition, platelets express surface receptors for factors Va and VIIIa and may facilitate their assembly with tissue factor and subsequent prothrombin activation and thrombin generation. Activated platelets also release activated factor V from their α granules, facilitate factor VIII activation by thrombin or factor X, and facilitate contact phase activation (factor XII and XI). All of these reactions indicate that the explosive generation of thrombin after coagulation activation relies on platelets.

The antithrombotic effect of abciximab is primarily attributable to the blocking of platelet GPIIb/IIIa receptors, but recent in vitro and ex vivo evidence suggests a possible direct antithrombin effect. Platelet inhibition with abciximab led to a nearly 50% decrease in thrombin potential in a gel-filtered platelet system and a platelet-rich plasma system when coagulation was initiated with tissue factor in the absence of heparin and aspirin. In ex vivo systems, treatment with GPIIb/IIIa inhibitors also led to a reduction in thrombus formation. In addition, in an ex vivo perfusion chamber containing severely injured arterial wall under the local rheologic conditions of a mildly stenosed coronary artery, thrombus formation was significantly reduced by abciximab and not by heparin. In patients undergoing interventional procedures, treatment with abciximab and even tirofiban was associated with a decrease in prothrombin activation and thrombin generation during the procedure compared with patients receiving only heparin and aspirin. In all of these studies, prothrombin activation was measured immediately after bolus administration and at the end of the procedures. No data are available concerning the effect of abciximab on in vivo markers of prothrombin activation and thrombin generation in patients with unstable angina or non–Q-wave myocardial infarction not undergoing interventional procedures during prolonged 24- or 48-hour infusion.

Our data show that abciximab has no effect on plasma prothrombin activation or thrombin generation in this context. F1 + 2 is a sensitive marker of prothrombin activation. Its value in identifying increased hemostatic system activity and its response to antithrombotic treatment has been confirmed in various clinical settings. F1 + 2 levels therefore seem to be an adequate marker for monitoring the effect of drugs on prothrombin activation in vivo. Support for an in vivo anticoagulant effect of abciximab comes from an analysis of activated clotting times (ACT) in the EPIC study. Moliterno et al reported that although they received similar doses of heparin, the patients treated with abciximab had longer ACTs than those treated with placebo. In their study, ACTs during treatment were measured in patients undergoing high-risk interventional procedures who received 12-hour abciximab infusion and high heparin doses (target ACT >300 sec). Furthermore, this was a high-risk population that was likely to have a high thrombus burden and a consequently increased level of thrombin generation. The absence of any effect on prothrombin activation and thrombin generation in our study may depend on the fact that the study population may have included patients with a minor thrombotic component and that the study drug was given on top of heparin and aspirin treatment. The results may have been different in patients with a higher thrombus burden. Most of our patients had normal prothrombin activation and thrombin generation levels, and abciximab may be ineffective in additionally reducing normal levels of thrombin generation. Previous studies have shown that the efficacious inhibition of prothrombin activation may depend on the levels of prothrombin activation at baseline and that abciximab therapy during interventional procedures reduces thrombin generation and activity only in higher risk patients, who are likely to have a greater thrombus burden and higher levels of thrombin generation.

Finally, a possible explanation for the lack of effect of abciximab on prothrombin activation and thrombin generation in our study may be an inadequate antithrombin effect because of the fact that lower doses of heparin were used than those given in studies performed during interventional procedures. In vitro studies have shown that there is a steep relationship between receptor blockade and the inhibition of thrombin generation; at higher doses, there was a linear relationship that reached a plateau at 50% thrombin generation inhibition and 90% receptor blockade. Although phar-

### TABLE 4. Median TAT Plasma Levels (25th to 75th Percentiles) in the 3 Treatment Groups (ng/mL)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (n=56)</th>
<th>24-h Abciximab (n=52)</th>
<th>48-h Abciximab (n=59)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline TAT</td>
<td>2.8 (2.2–4.3)</td>
<td>3.0 (2.4–4.5)</td>
<td>3.5 (2.5–5.8)</td>
<td>NS</td>
</tr>
<tr>
<td>24-h TAT</td>
<td>3.1 (2.4–5.2)</td>
<td>2.9 (1.9–4.4)</td>
<td>3.2 (2.2–5.4)</td>
<td>NS</td>
</tr>
<tr>
<td>48-h TAT</td>
<td>3.5 (2.3–7.3)</td>
<td>3.1 (2.1–6.4)</td>
<td>3.7 (2.2–7.9)</td>
<td>NS</td>
</tr>
<tr>
<td>1-mo TAT</td>
<td>3.2 (2.2–5.7)</td>
<td>3.6 (2.5–6.3)</td>
<td>2.9 (2.1–5.3)</td>
<td>NS</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

The median and 25th and 75th percentiles of the plasma TAT levels at the different time points are shown in Table 4. There was no change in TAT levels after 24 hours (median change 0 ng/mL; –1.2 to 2.2) or 48 hours (median change 0; –0.87 to 2.2). After 1 month, the levels were similar to those found at baseline (median change 0.1 ng/mL, –1.47 to 0.67).

### Between-Group Comparison

After 24 and 48 hours and 1 month, there was no difference in the plasma levels of either F1 + 2 or TAT in the 3 treatment groups and no difference in the median change of the 2 markers between the baseline and the 24- or 48-hour determinations. Even when the patients were stratified on the basis of the presence of abnormal baseline F1 + 2 levels, the fact that they were not receiving heparin at randomization, or whether they had a positive troponin I test at admission, the effect of abciximab on the coagulation activation markers was similar in the 3 treatment groups (data not shown).

### Discussion

We evaluated the effect of 24- or 48-hour abciximab infusions on prothrombin activation and thrombin generation in patients with acute coronary syndromes without ST-segment elevation not undergoing interventional procedures.

It is well known that activated platelets accelerate thrombin generation by 5 to 6 orders of magnitude. Platelet activation leads to the surface exposure of phosphatidylserine and other anionic phospholipids normally concentrated in the inner leaflet of the membrane bilayer, which form the basis on which coagulation reactions occur. In addition, platelets express surface receptors for factors Va and VIIIa and may facilitate their assembly with tissue factor and subsequent prothrombin activation and thrombin generation. Activated platelets also release activated factor V from their α granules, facilitate factor VIII activation by thrombin or factor X, and facilitate contact phase activation (factor XII and XI). All of these reactions indicate that the explosive generation of thrombin after coagulation activation relies on platelets.

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macokinetic and pharmacodynamic data concerning 24-hour abciximab infusion show that only a very small minority of patients do not reach high levels of platelet inhibition (unpublished data), it is possible that the prolongation of standard-dose therapy in patients receiving lower heparin doses than those used during interventional procedures meant that at least some of the patients had an insufficient level of platelet inhibition after 48 hours to prevent residual platelet activity from sustaining prothrombin activation and thrombin generation. We cannot exclude the possibility that had we taken an early sample immediately after bolus administration or during the first hours of treatment, we would have observed a decrease that was not detectable later. Furthermore, abciximab and PCI may have synergistic effects insofar as the procedure can alter plaque rheology and elicit a controlled plaque rupture, and abciximab prevents the platelet deposition that could lead to prothrombin activation. In the absence of traumatic procedural injury and vessel wall remodeling, the effect may not be detectable.

On the other hand, our data exclude a prothrombotic effect of prolonged abciximab infusion, because there was a similar increase in thrombin generation after 48 hours in all 3 groups, which was confirmed after 1 month. This is in keeping with previous studies showing a progressive increase in prothrombin F1 + 2 levels after the acute event even with high doses of heparin. This may reflect the persistence of an active thrombotic process, which has been shown at angiography, and the presence of still active disease after the acute event attributable to mechanisms not influenced by heparin or even high levels of platelet inhibition.

In conclusion, prolonged abciximab infusion does not attenuate prothrombin activation and thrombin generation in patients with acute coronary syndromes without ST elevation receiving heparin and aspirin and with laboratory signs of a low thrombin burden who are not undergoing interventional procedures. Whether abciximab may reduce these parameters in patients with higher levels of procoagulant activity still needs to be investigated.

References
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_Circulation_. 2002;105:928-932; originally published online February 4, 2002;
doi: 10.1161/hc0802.104456
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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