Emergency Administration of Abciximab for Treatment of Patients With Acute Ischemic Stroke
Results of a Randomized Phase 2 Trial

Abciximab Emergent Stroke Treatment Trial (AbESTT) Investigators*

Background and Purpose—Because of its success in treatment of acute cardiac ischemia, there is interest in the use of abciximab for treating patients with acute ischemic stroke. A previous dose-escalation study determined that abciximab could be given safely in a regimen of 0.25 mg/kg intravenous bolus followed by a 12-hour infusion at 0.125 μg/kg per minute (maximum 10 μg/min). This study was performed to obtain more information about the safety and potential efficacy of abciximab in patients with stroke.

Methods—An international randomized, double-blind, placebo-controlled phase 2 trial enrolled 400 patients within 6 hours of onset of ischemic stroke. The primary safety outcome was the rate of symptomatic hemorrhage that occurred during the first 5 days after stroke. The primary efficacy measure was the distribution of outcomes at 3 months after stroke using the modified Rankin Scale (mRS) based on an ordinal regression model of outcomes, adjusting for baseline severity of stroke, age, and interval from stroke.

Results—Symptomatic intracranial hemorrhage within 5 days was diagnosed in 7 of 195 (3.6%) patients treated with abciximab and 2 of 199 (1%) patients given placebo (odds ratio [OR], 3.7; \( P = 0.09 \); 95% confidence interval [CI], 0.7 to 25.9). Asymptomatic hemorrhagic transformation was detected by brain imaging in 24 patients administered abciximab and 33 patients receiving placebo (OR, 0.74; \( P = 0.25 \); 95% CI, 0.4 to 1.3). Treatment with abciximab showed a nonsignificant shift in favorable outcomes as measured by mRS scores at 3 months (OR, 1.20; \( P = 0.33 \); 95% CI, 0.84 to 1.70).

Conclusions—Intravenously administered abciximab can be given to patients with a reasonable degree of safety. The trial also suggests that abciximab could improve outcomes at 3 months after stroke. A larger randomized, double-blind, placebo-controlled trial is necessary to test the efficacy of abciximab. (Stroke. 2005;36:880-890.)

Key Words: antiplatelet agents ■ emergency medical treatment ■ stroke

Only intravenously administered recombinant tissue plasminogen activator (rtPA) is established as effective for treatment of patients with acute ischemic stroke.1,2 Although effective, thrombolytic therapy has a low utility in the real-life setting because of the low number of patients treated. Among the reasons for the nonuse of rtPA are the short time window for administration and concerns about the potential for serious intracranial bleeding. In addition, recurrent occlusion leading to neurological worsening can occur after administration of rtPA.3 Recurrent occlusion might be secondary to procoagulant effects of rtPA, and therapies to counteract these actions are needed.4 Hence, there is a need for reperfusion agents that could be safely administered in a longer time window.

Activation of platelets is a key component of acute thromboembolism and experimental studies already demonstrate that interactions of platelets, inflammatory cells, and endothelial cells can affect perfusion.5,6 Two large trials have evaluated aspirin given within 48 hours of stroke.7,8 Whereas aspirin is recommended for treatment of patients with recent ischemic stroke, it is a weak acute antithrombotic agent and cannot be considered as a substitute for reperfusion treatment including rtPA.9

Acute blockade of the platelet glycoprotein IIb/IIIa receptor reduces ischemic complications after percutaneous coronary intervention, and preliminary data in ischemic stroke have been encouraging with abciximab.9–14 Abciximab is a chimeric mouse/human monoclonal antibody with high binding affinity for the platelet glycoprotein IIb/IIIa receptor; it also exerts cross-reactivity with other integrins such as the endothelial αv/β3 receptor and the leukocyte Mac-1 integrins.15,16 Zhang et al17 documented reduction in infarct...
volume and improved functional recovery in rodents given abxicimab in conjunction with rtPA. They attributed these effects to enhancement of the patency and integrity of the cerebral microvasculature. In a study of patients undergoing carotid angioplasty and stenting, Kopp et al.\(^{18}\) found that abxicimab was effective in limiting thrombus propagation by reducing interactions between platelets and monocytes. Abxicimab also has been given to patients undergoing cerebrovascular procedures and to some patients with ischemic stroke or acute intracranial arterial occlusions.\(^{19-27}\) Morris et al.\(^{28}\) successfully administered abxicimab and half-dose rtPA to 5 patients with acute ischemic stroke. Lee et al.\(^{24}\) gave the combination of intra-arterial urokinase and intravenous abxicimab to 10 patients. These patients had a higher rate of recanalization and better functional outcomes than did 16 patients who received only urokinase. Eckert et al.\(^{29}\) successfully treated 3 patients with intra-arterial rtPA and abxicimab. Some of the studies have reported a potential increase in risk in bleeding side effects.\(^{25-26}\) A dose-escalation study in 74 patients found that abxicimab could be given safely to a broad spectrum of patients treated within 24 hours of ischemic stroke.\(^{30-31}\) Because bleeding is a potential complication of treatment with abxicimab, even in the absence of concomitant thrombolytic therapy, we performed the Abciximab in Emergent Stroke Treatment Trial (AbEStT) to obtain more information about the safety of the medication. In addition, if the agent demonstrated evidence for potential efficacy, the results of the AbEStT could be used to develop a larger clinical trial to test the effectiveness of the agent.

**Materials and Methods**

AbEStT is an international randomized, double-blind, placebo-controlled phase 2 trial that tested intravenously administered abxicimab given within 6 hours of onset of stroke in carefully selected patients. The primary safety aim of the study was to evaluate the rate of symptomatic (fatal or nonfatal) intracranial hemorrhage that occurred within 5 days or hospital discharge, whichever was sooner (referred as day 5/discharge from now on). The assumption was that more patients administered abxicimab would have symptomatic hemorrhages than would the placebo-treated patients. Secondary safety outcomes included asymptomatic intracranial hemorrhage detected on brain imaging within 5 days, major nonintracranial hemorrhage within 5 days, thrombocytopenia within 5 days, or deaths within 3 months. A sample size of 400 patients (200 in each group) was selected to detect an odds ratio (OR) of 3.25 in symptomatic hemorrhage rate with an estimated proportion of 0.05 using an alpha of 0.05 and power of 0.90.

The primary efficacy aim was a comparison of outcomes at 3 months assessed by the modified Rankin Scale (mRS).\(^{32}\) The range of scores was compared between the 2 treatment groups. The null efficacy hypothesis was that the distribution of 3-month mRS scores would be the same for patients assigned treatment with abciximab and those given placebo, when adjusting for baseline covariates of baseline National Institutes of Health Stroke Scale (NIHSS) score, age, and interval from stroke until treatment. The alternative hypothesis was that a difference in distribution of mRS scores favoring treatment with abciximab would be similar to that found with intravenous rtPA.\(^{1}\) A secondary analysis evaluated neurological recovery as measured by scores using the NIHSS at 5 days and 3 months.\(^{33}\) In addition, we looked at the number of patients in each treatment group that had mRS score of 0 or 1 at 5 days and 3 months. The latter comparison was the most important secondary endpoint.

A prespecified responder analysis, which judged favorable outcomes based on the baseline NIHSS score, was also performed.\(^{34}\) In this analysis, patients with a NIHSS score of 4 to 7 needed to reach a mRS score of 0; for those with scores of 8 to 14, the mRS score was 0 to 1; and for patients with ≥15 NIHSS scores, a mRS score of 0 to 2 was considered as a favorable response. Other efficacy outcomes included the frequency of neurological worsening (stroke progression) as measured by NIHSS scores at 5 days or recurrent strokes within 3 months.

**Patients**

Patients older than 18 years with acute ischemic stroke and who could be treated within 6 hours of onset of symptoms were eligible. Their baseline NIHSS score had to be ≥4 and <23. These limits were similar to those used in the dose-escalation study. Baseline screening included a clinical evaluation, noncontrast-enhanced computed tomographic (CT) scan of the brain, and laboratory tests. The respective institutional human research committees had approved the protocol and consent. Before entry, a consent was signed by either the patient or surrogate (next-of-kin) when permitted by regulatory authorities.

Exclusion criteria were similar to those used in other trials testing acute therapies for treatment of ischemic stroke. The leading reasons for exclusion are listed in Table 1. Patients, who might otherwise be treated with intravenous thrombolysis, including most patients seen within 3 hours of onset of stroke, were to be excluded.

**Randomization, Treatment Regimen, and Ancillary Care**

Randomization was at a ratio of 1:1 (abciximab or placebo) with stratification on the basis of baseline severity of stroke (NIHSS score 4 to 14 or 15 to 22) and clinical site. Pharmacists at the sites dispensed abxicimab or identical-appearing placebo. The dosage of the bolus of abxicimab was 0.25 mg/kg. It was followed by a 12-hour infusion at a rate of 0.125 µg/kg per minute (maximum infusion was 10 µg/min). After completion of a follow-up CT at 36 to 48 hours after the end of the infusion, patients were subsequently treated with aspirin or other antithrombotic medications at the discretion of the treating physician. Mechanical measures to prevent deep vein thrombosis among bedridden patients were allowed during the treatment period.

**Follow-up Clinical and Laboratory Assessments**

The baseline clinical evaluation included prestroke mRS score, Barthel Index score, and NIHSS score.\(^{35}\) Investigators performed daily scoring of the NIHSS through day 5 or discharge, whichever

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**Table 1. Most Common Reasons for Exclusion for Patients Not Enrolling in AbEStT**

<table>
<thead>
<tr>
<th>Reason</th>
<th>No.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset of symptom impossible to determine</td>
<td>533</td>
</tr>
<tr>
<td>Severity of neurological impairments &lt;4 points on NIHSS or symptoms rapidly resolving</td>
<td>2166</td>
</tr>
<tr>
<td>Severity of neurological impairments &gt;22 points on NIHSS</td>
<td>255</td>
</tr>
<tr>
<td>CT findings of hemorrhage</td>
<td>441</td>
</tr>
<tr>
<td>&gt;50% middle cerebral artery territory or baseline CT or signs of increased intracranial pressure</td>
<td>83</td>
</tr>
<tr>
<td>Disabled before stroke (Barthel Index or Rankin Scale)</td>
<td>163</td>
</tr>
<tr>
<td>Received rtPA for stroke (&lt;3 h)</td>
<td>719</td>
</tr>
<tr>
<td>Persistent hypertension that cannot be controlled</td>
<td>83</td>
</tr>
<tr>
<td>Coagulation abnormality on baseline tests</td>
<td>136</td>
</tr>
<tr>
<td>Recent major hemorrhage, surgery, or trauma</td>
<td>153</td>
</tr>
<tr>
<td>Concomitant severe medical illness</td>
<td>262</td>
</tr>
<tr>
<td>Need for contraindicated surgical or medical therapies</td>
<td>264</td>
</tr>
</tbody>
</table>

*Many patients had >1 exclusion criterion.

CT indicates computed tomography; NIHSS, National Institutes of Health Stroke Scale.
Role of Funding Sources and Overall Conduct of the Trial

This trial was funded through research grants from Eli Lilly and Centocor. The trial was designed as a registration study to submit to the US Food and Drug Administration to support a marketing approval for abciximab for treatment of patients with ischemic stroke. Representatives of Eli Lilly and Centocor participated in the design and conduct of the trial. They also served as ex-officio members of the Steering and Publications Committees. Representatives of the sponsors performed on-site monitoring of the data and patient records for quality assurance and regulatory reporting. Interim and final data analyses were performed by the Data Management Center at Centocor. The investigators had the opportunity to probe the database and to independently review the results of the analyses.

A steering committee with co-principal investigators from Europe and North America (Werner Hacke, MD and Harold P. Adams Jr, MD) supervised the trial. Clinical coordinating centers were located in Heidelberg, Germany and Iowa City, Iowa. Participating sites, with the number of enrolled patients and key members of the research teams, are listed in the Appendix. Assignment of treatments was via a central telephone system coordinated at Nottingham Clinical Research, United Kingdom. Data were submitted using provided case report forms. Copies of brain imaging studies also were submitted to the University of Iowa for independent blinded review by a panel of neuroradiologists. Another independent adjudication panel (Clinical Endpoint Committee) blindly reviewed all potential safety endpoints, deaths, or cases of possible recurrent or progressing stroke. All individual safety reports and interim analyses were shared with an independent external safety monitoring committee.

A publications committee (Appendix) is responsible for reporting the scientific data and the writing of this article. The sponsors had the opportunity to review this publication before submission for the purpose of ensuring the medical accuracy of the data reported and to determine if documents needed to be filed to protect the intellectual property interests in the compound or its uses.

Statistical Plans

All efficacy analyses were conducted on an intent-to-treat basis, as defined by treatment assignment group, whereas safety analyses were performed only on data from patients who actually received the study agent, a strategy that is commonly used in large clinical trials. During the design of the trial, available data did not provide sufficient evidence about the direction of the effects of abciximab on the endpoints to justify the use of 1-sided testing and, as a result, 2-sided probability values were calculated. Fisher exact test was used to compare the rates of intracranial hemorrhage, recurrent stroke, or stroke progression. Other dichotomous safety endpoints were compared between treatment groups using $\chi^2$ tests. Three-month mortality rate was performed using Kaplan–Meier mortality estimation based on those deaths that occurred within 120 days of randomization. Mortality was analyzed using a logrank test between the 2 groups.

All analyses for efficacy were performed on the intention-to-treat population, regardless of whether study medication was administered. For patients with missing outcome data, the last observation carried forward was used. The primary efficacy analysis used an ordinal logistic regression model (proportional odds or cumulative logit model) described by Agresti. This analysis compared the distribution of 3-month mRS scores between treatment groups, both unadjusted and adjusted for baseline NIHSS score, the time from onset of stroke until treatment, age, and time to follow-up. A Wald $\chi^2$ test from the multivariate regression model was used to compare the treatment effect on the distribution of mRS scores at 3 months. Analyses of secondary endpoints were not adjusted for baseline covariates. Odds ratios were estimated by the Mantel–Haenszel method and the 95% confidence limits were calculated using the procedures developed by Robins, Breslow, and Greenfield.
Results

Overall Study Performance

Between May 2000 and February 2002, 401 patients (200 in placebo group) were enrolled in 38 sites in Europe and North America (Figure 1). One patient (assigned abciximab) immediately withdrew consent and was withdrawn from the study. This patient would not permit use of any data, including those collected at baseline. During the enrollment period, 5342 patients were screened. The primary reasons for exclusion are listed in Table 1. Many patients had >1 reason for exclusion.

Six patients did not receive treatment (abciximab, 5; placebo, 1), largely as the result of detection of an exclusion criterion after enrollment; the most common reason was hypertension. Approximately one-half of the patients were treated >5 hours after onset of stroke. (Table 2). Study agent was started after 6 hours in 13 patients (abciximab, 5; placebo, 8). Delays in treatment, which were largely attributed to logistical issues, ranged from 3 to 63 minutes (median, 17 minutes).

Study agent was halted before the end of the 12-hour infusion in 9 patients (Figure 1). Reasons for premature stopping of the infusion were bleeding in 3 abciximab-treated patients (2 intracranial bleeding) and thrombocytopenia in 1 placebo-treated patient. Two placebo-treated patients had study agent halted because of hypertension. An investigator broke the study allocation (blind) for 1 placebo-treated patient.

Twenty-six patients (abciximab, 14) received another antithrombotic medication, most commonly aspirin, after enrollment and before the 24-hour to 36-hour follow-up CT examination. Subsequently, antithrombotic medications administered within 5 days of stroke included aspirin for 209 patients (abciximab, 105), clopidogrel for 60 (abciximab, 26), dipyridamole for 13 (abciximab, 5), oral anticoagulants for 46 (abciximab, 21), and heparin or low-molecular-weight heparins for 79 (abciximab, 32).

Follow-up assessments within the desired time window of 3 months were obtained in 385 patients (abciximab, 195), including those patients who had died. Fifteen patients (abciximab, 5) had the last observation carried forward to 3 months. Three patients returned after the 120-day window; the final analyses used the scores obtained at the last visit within the 120-day window and not the scores that were obtained later. The treatment assignments and the earlier and subsequent mRS scores were (#1 placebo, 3/1; #2 placebo, 4/4; and #3 abciximab, 3/2). Two patients (abciximab, 1) were known to be alive but refused to return for assessments. The local sites could not arrange a follow-up visit for 3 placebo-treated patients who were known to be alive. Five patients (abciximab, 1) were lost to follow-up. The only data from 1 patient in the abciximab group were collected at
TABLE 2. Baseline Characteristics of Enrolled Patients

<table>
<thead>
<tr>
<th></th>
<th>Abciximab n=200</th>
<th>Placebo n=200</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>67±13.6</td>
<td>68±12.8</td>
</tr>
<tr>
<td>Men</td>
<td>120 (60)</td>
<td>105 (52.5)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>177 (88.5)</td>
<td>179 (89.5)</td>
</tr>
<tr>
<td>Black</td>
<td>19 (9.5)</td>
<td>11 (5.5)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (2.0)</td>
<td>10 (5.0)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>122</td>
<td>116</td>
</tr>
<tr>
<td>North America</td>
<td>78</td>
<td>84</td>
</tr>
<tr>
<td>Mean weight, kg</td>
<td>76.5 kg±15.8</td>
<td>76.7 kg±15</td>
</tr>
<tr>
<td>Mean interval from stroke until randomization</td>
<td>4.5 h±0.9</td>
<td>4.5 h±1</td>
</tr>
<tr>
<td>Mean interval from randomization to treatment</td>
<td>31.2 min±16.7</td>
<td>32.9 min±18.1</td>
</tr>
<tr>
<td>Treated &lt;3 h</td>
<td>7 (3.5)</td>
<td>7 (3.5)</td>
</tr>
<tr>
<td>Treated 3–6 h</td>
<td>183 (91.5)</td>
<td>184 (92)</td>
</tr>
<tr>
<td>Treated &gt;6 h</td>
<td>5 (2.5)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Mean NIHSS score</td>
<td>9.7±5.1</td>
<td>10.2±4.8</td>
</tr>
<tr>
<td>Median NIHSS score</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>NIHSS score 4–7</td>
<td>92 (46)</td>
<td>75 (37.5)</td>
</tr>
<tr>
<td>Score 8–14</td>
<td>64 (32)</td>
<td>79 (39.5)</td>
</tr>
<tr>
<td>Score 15–22</td>
<td>44 (22)</td>
<td>46 (23)</td>
</tr>
<tr>
<td>Baseline CT findings</td>
<td>199 scans available</td>
<td>198 scans available</td>
</tr>
<tr>
<td>Signs of new stroke</td>
<td>41 (20.6)</td>
<td>49 (24.7)</td>
</tr>
<tr>
<td>Signs of old stroke</td>
<td>78 (39.2)</td>
<td>67 (33.8)</td>
</tr>
<tr>
<td>Selected medications within 7 days before stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>70 (35.0)</td>
<td>73 (36.5)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>11 (5.5)</td>
<td>7 (3.5)</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>2 (1.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>6 (3.0)</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>Calcium blocker</td>
<td>25 (12.5)</td>
<td>33 (16.5)</td>
</tr>
<tr>
<td>Other BP medication</td>
<td>89 (44.5)</td>
<td>100 (50.0)</td>
</tr>
<tr>
<td>Adjudicated TOAST cause of stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>44 (22)</td>
<td>53 (26.5)</td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>31 (15.5)</td>
<td>34 (17.0)</td>
</tr>
<tr>
<td>Small vessel occlusion</td>
<td>29 (14.5)</td>
<td>19 (9.5)</td>
</tr>
<tr>
<td>Other cause</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>95 (47.5)</td>
<td>93 (46.5)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>120 (60)</td>
<td>132 (66)</td>
</tr>
<tr>
<td>Mean systolic blood pressure</td>
<td>152.2 mm Hg (±21.6)</td>
<td>151.7 mm Hg ±21.5</td>
</tr>
<tr>
<td>Mean diastolic blood pressure</td>
<td>80.2 mm Hg (±14.1)</td>
<td>79.9 mm Hg ±15</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>51 (25.5)</td>
<td>42 (21)</td>
</tr>
<tr>
<td>Baseline serum glucose, mean</td>
<td>7.8 mmol±3.8</td>
<td>7.9 mmol±3.5</td>
</tr>
<tr>
<td>Current smoking</td>
<td>63 (31.5)</td>
<td>49 (24.5)</td>
</tr>
<tr>
<td>Past smoking</td>
<td>35 (17.5)</td>
<td>45 (22.5)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>21 (10.5)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>21 (10.5)</td>
<td>30 (15)</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>31 (15.5)</td>
<td>21 (10.5)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>28 (14)</td>
<td>27 (13.5)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure (antihypertensive) medication; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Either insulin dependent or non-insulin dependent diabetes mellitus
baseline; as a result, the last mRS score was the prestroke value (Figure 1).

Baseline Features
Overall, baseline characteristics were similar in the 2 treatment groups (Table 2). No significant differences were found in regard to epidemiological factors, interval from stroke, laboratory assessments, brain imaging studies, or previous use of medications. The stratification assured that the numbers of more seriously affected patients (NIHSS score >14) were equal in the 2 treatment groups. However, a difference in severity of strokes was noted among those patients with lower NIHSS scores (Table 2). Ninety-two patients in the abciximab group had scores of 4 to 7, whereas 75 patients in the placebo group had such scores. The mean NIHSS scores for the abciximab-treated and placebo-treated patients were 9.7 and 10.2, respectively (P = 0.32). The median NIHSS scores for the abciximab-treated and placebo-treated patients were 8 and 9 (P = 0.19). The subtypes of stroke listed in Table 2 are those diagnosed in the external adjudication process.

Safety
Forty-three patients died during the follow-up period; 10 patients (abciximab, 8) died during the first 5 days (Table 3). No significant difference in mortality was observed (log-rank test P = 0.27). The leading causes of death were related to the qualifying stroke, including brain edema, medical complications of the stroke, or heart disease. Ten patients in the placebo group and 5 in the abciximab group died as a result of the initial stroke. Although 2 patients (1 in each group) died after the diagnosis of a symptomatic hemorrhagic transformation, neither death was ascribed directly to the bleeding. Pneumonia was the cause of death in the patient treated with abciximab. A placebo-treated patient died from a recurrent stroke.

Intracranial Hemorrhages
Symptomatic intracranial hemorrhages occurred within 5 days of entry in 7 patients treated with abciximab (3.6%) (patients 3 and 5 to 10 in Tables 3 and 4 and Figure 2) and 2 patients treated with placebo (1%) (patients 1 and 2 in Tables 3 and 4 and Figure 2) (OR, 3.7; P = 0.09; 95% confidence interval [CI], 0.7 to 25.9). Figure 2 shows the locations and types of symptomatic hemorrhages. One case of symptomatic hemorrhage occurred in an abciximab-treated patient in the interval from day 5 to 3 months (patient 4). The locations of the symptomatic hemorrhage were within the area of the qualifying infarction in 9 patients (abciximab, 7). Extension of bleeding into another brain location was found in 1 patient treated with abciximab. Three abciximab-treated patients had intraventricular blood found on CT. The timing of the events, the changes in NIHSS scores, and the concomitant medications are described in Table 4. Five abciximab-treated and both placebo-treated patients had used aspirin within the 7 days before randomization. One abciximab-treated patient had received warfarin within 7 days of entry in the trial. None of the patients who had a symptomatic hemorrhage had a favorable outcome.

Other Bleeding, Thrombocytopenia, or Other Serious Adverse Events
Within the first 5 days, 3 placebo-treated patients had major (2) or minor (1) bleeding as defined by the modified TIMI classification. Eight abciximab-treated patients had bleeding events, and 3 were major. (Table 3). Thirty abciximab-treated and 45 placebo-treated patients had 1 or more other serious adverse experiences recorded during the first 5 days. Pneumonia was diagnosed in 8 patients (abciximab, 5). Five patients (abciximab, 4) had cardiac arrests. Four patients (2 in each group) had congestive heart failure. Four placebo-treated patients and none treated with abciximab had brain edema. Pulmonary embolism was diagnosed in 1 abciximab-
treated patient and 2 placebo-treated patients. One abciximab-
treated patient had myocardial ischemia diagnosed.

Neurological Worsening or Recurrent Stroke
Stroke progression was diagnosed within the first 5 days/
discharge in 14 abciximab-treated and 24 placebo-treated pa-
tients (P<0.12; OR, 0.56; 95% CI, 0.26 to 1.15). Neurological
worsening occurred within the first 48 hours in 12 abciximab-
treated and 20 placebo-treated patients (P=0.14; OR, 0.58; 95%
CI, 0.26 to 1.28). Recurrent strokes were diagnosed within 3
months in 7 abciximab-treated and 8 placebo-treated patients
(P=1.0; OR, 0.87; 95% CI, 0.28 to 2.70).

Outcomes at 3 Months
The ordinal regression model of mRS scores adjusted for the
baseline variables found a nonsignificant shift of mRS scores

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**TABLE 4. Cases of Symptomatic Intracranial Hemorrhage**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Agent</th>
<th>Interval to SH</th>
<th>Other Medications</th>
<th>NIHSS Scores</th>
<th>mRS Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>At Time of Bleeding</td>
<td>After Bleeding</td>
</tr>
<tr>
<td>1</td>
<td>68</td>
<td>P</td>
<td>2 d</td>
<td>None</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>P</td>
<td>24 h</td>
<td>A,C, subcut. H</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>Ab</td>
<td>2 d</td>
<td>H</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>Ab</td>
<td>16 d</td>
<td>A, W</td>
<td>15</td>
<td>N/A†</td>
</tr>
<tr>
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A indicates aspirin; Ab, Abciximab; C, clopidogrel; H, heparin; mRS, modified Rankin scale; N/A, not applicable; P, placebo; subcut, subcutaneously administered; W, warfarin or other oral anticoagulant.

*Patient 9 had received heparin prior to administration of study agent.
†NIHSS Score in patient 4 not calculated because patient was comatose. Patient 8 had improved from baseline and then worsened on day 4.

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**Figure 2.** Brain imaging findings in 10 cases of symptomatic intracranial hemorrhage. These studies show the pattern, extent, and location of the hemorrhages that were adjudicated as being symptomatic.
in favor of treatment with abciximab (P=0.33; OR, 1.2; 95% CI, 0.84 to 1.70). This result, which reflects the numbers of patients in each category of the mRS (Figure 3), was the primary efficacy analysis. The unadjusted ordinal regression also was in favor of abciximab (P=0.06; OR, 1.39; 95% CI, 0.98 to 1.97).

The ranges of mRS scores in the 2 treatment groups are shown in Figure 3. At 3 months, 97 of 200 patients (48.5%) assigned to treatment with abciximab had a mRS score of 0 or 1 compared with 80 of 200 patients (40%) in the placebo (P=0.09; OR, 1.41; 95% CI, 0.95 to 2.10). This result is not adjusted to baseline NIHSS score, age, or interval from stroke until treatment.

By 3 months, the percentage of responders (rates of favorable outcomes as influenced by baseline NIHSS score) was higher with abciximab (73/200, 36.5%) than with placebo (54/200, 27%) (Mantel–Haenszel P=0.04; Mantel–Haenszel OR, 1.60; 95% CI, 1.012 to 2.38). Neurological improvement by day 5/discharge was diagnosed in 98 of 200 (49%) abciximab-assigned patients and in 77 of 200 (38.5%) (P=0.03; OR, 1.54; 95% CI, 1.01 to 2.33). Neurological recovery by day 5 (NIHSS 0 to 1) was found more frequently with abciximab (57/200, 28.5%) than with placebo (33/200, 16.5%) (P=0.004; OR, 2.02; 95% CI, 1.21 to 3.38). At 3 months, 46% (92/200) of abciximab-treated patients had NIHSS scores of 0 to 1, whereas 34% (68/200) placebo-treated patients had these scores (P=0.01; OR, 1.65; 95% CI, 1.10 to 2.48). At 3 months, 57.5% (115/200) of patients in the abciximab-assigned group had scores of 95 to 100 on the Barthel Index and 50.5% (101/200) of placebo-treated patients had similar outcomes (P=0.16; OR, 1.33; 95% CI, 0.89 to 1.97). The frequencies of favorable outcomes among the placebo and abciximab-treated groups as influenced by the baseline stratification variable for severity of impairments and rates of favorable outcomes as influenced by baseline severity of stroke using the responder analysis are shown in Figure 4.

**Discussion**

AbESTTT is a preliminary trial testing a promising therapy for treatment of acute ischemic stroke. It used components of modern clinical trial design and conduct to achieve an unbiased evaluation of the safety and potential efficacy of abciximab. The design of the trial included 2-sided tests to provide a cautious estimate of differences in responses to treatment. This testing strategy is appropriate to not falsely conclude a finding in a phase 2 trial such as AbESTTT. Such an approach also is compatible with current regulatory guidance. The criteria for entry of patients were similar to those included in other acute stroke trials. The demographic factors are representative of a population of patients with acute stroke; thus, the results of AbESTTT can be compared with those achieved with other trials testing promising therapies for acute stroke. Although we did attempt to achieve homogeneity in the severity of strokes between the 2 treatment groups using the NIHSS score as a stratification variable, we did have an important difference in baseline severity of stroke using the responder analysis are shown in Figure 4.
scores among the patients with less severe strokes. This disparity in stroke severity probably is secondary to the relatively small size of the trial.

The trial was designed to test the safety of abciximab in a regimen that is used to treat patients with myocardial ischemia and is based on the results of a previously performed dose-escalation study.11,12,30 Rather than administering the agent in combination with anticoagulants, other antiplatelet agents, or thrombolytic medications, as is the usual course of therapy with acute myocardial ischemia, the trial tested abciximab without the simultaneous administration of other antithrombotic agents primarily because of concerns about the potential for bleeding.

Early reconstitution of blood flow appears to be critical for successful treatment of stroke. However, the short interval for safe and effective administration of rtPA is one of the major limitations of this therapy. Therefore, one of the goals of this study was to test the safety and potential efficacy of another intravenous agent that affects perfusion and that could be administered >3 hours after stroke. We limited enrollment to patients who could be treated within 6 hours of stroke, a time window that is similar to that employed in a trial of intra-arterial thrombolysis.45

The trial tested the potential usefulness of abciximab when the agent was added to best medical treatment. The control group received placebo. The use of placebo is scientifically and ethically justified because only rtPA is established as effective in improving outcomes after stroke. The trial emphasized that patients who could be treated with rtPA should receive this medication instead of being enrolled. However, for those centers where thrombolytic therapy was not available, treatment within 3 hours of stroke was permitted and 14 patients did receive study agent in this time period. We have no evidence that patients who could have been treated with rtPA were shunted into the trial. As the result of these steps, the results of AbESTT largely reflect treatment of patients at stroke onset, these results are particularly relevant to the large majority of patients in this trial were treated from 8% to 12% (Figure 4).

In AbESTT, most bleeding events were detected within the first 48 hours of treatment, an experience that is similar to that noted with thrombolytic therapy.46 Eight of the 10 cases of symptomatic intracranial bleeding were among the group of patients with larger strokes. This finding is similar to that found with use of rtPA or anticoagulants.47,48 Just as with administration of other medications with potent effects on coagulation, our experience suggests that caution should be exercised when given abciximab to seriously affected patients. Some of the symptomatic hemorrhages occurred among patients who received other antithrombotic medications either before entry into the trial or after the initial treatment period. Such occurrences support our decision to test the safety of abciximab administered without other agents that affect coagulation during the acute treatment period. The rates of other serious bleeding complications or thrombocytopenia were low. Mortality was not increased among the patients treated with abciximab. This trial shows that abciximab can be administered within 6 hours of stroke to a broad spectrum of patients with a reasonable assurance for safety.

Because of the relatively small sample size, the investigators did not expect the trial to provide definitive data about the usefulness of abciximab in treatment of patients of stroke. Still, AbESTT provides the opportunity to look at a trend for potential efficacy of the agent. We included an ordinal regression model to take into account the range of mRS scores and the data, when adjusted for important variables including age, interval until treatment, and severity of stroke, provide a hint that abciximab is associated with improved outcomes at 3 months. In addition, we prespecified several other efficacy analyses based on dichotomous endpoints, such as the percentage of patients with mRS scores of 0 to 1 at 3 months. We are encouraged by the results when one considers that the agent was given up to 6 hours after onset of stroke and no other intravenously administered therapy has been established as useful in this time period. We also found a trend in favor of treatment using the responder analysis, which adjusted desired outcomes in response to baseline NIHSS score. We noted improvement with treatment among those patients with mild-to-moderately severe stroke. The absolute differences in rates of favorable outcomes ranged from 8% to 12% (Figure 4).

The efficacy results of this study need to be interpreted with care because the number of patients enrolled in AbESTT is relatively small. Our experience with abciximab for treatment of acute ischemic stroke still is limited. AbESTT does not establish the efficacy of abciximab in improving outcomes when it is administered within 6 hours of onset of acute ischemic stroke. We also should take into consideration that an important difference in baseline characteristics (baseline severity of stroke) was apparent between the 2 groups. Some of the success of abciximab treatment might be secondary to treating less seriously affected patients. However, the results of this trial suggest that the agent might be both beneficial and safe, particularly among patients with mild-to-moderate stroke. Given that the majority of patients in this trial were treated >3 hours after stroke onset, these results are particularly relevant to the large number of patients who arrive too late for treatment with intravenous rtPA.
Appendix

Participating Sites (Principal investigators [PI], Co-investigators [CI], and Coordinators [SC]) listed by the number of patients enrolled:

Girona, Spain (n=32) A. Dávalos (PI); Y. Silva, M. Castellanos, J. Serena, L. Ramí (CI); M. Puigdemont (SC); Edmonton, AB (n=29) A. Shuaib (PI); N. Amir, N. Dean, K. Khan, M. Muratoglu, M. Saqour (CI); E. Kradibasic, D. Burridge, Z. Dean, E. Rudd, K. Tariq, S. Wedderburn (SC); Heidelberg, Germany (n=26) W. Hacke (PI); P. Ringleb, R. Weber, F. Buggle, R. Kollim, S. Rieger, C. Schrann, S. Külken, C. Berger, J. Bardutzki, K. Glatz, J. von Engelhard, C. Schim (PI); L. Raessler (SC); Marshallfield, WI (n=1) K. Madden (PI); P. Karianca, E. St. Louis (CI); K. Manc (SC); Winsion Salen, NC (n=1) P. Reynolds (PI); C. Tegeler, D. Leftkowitz, J. Greenberg, F. Khan, G. Wittenberg, C. O’Donovan, I. Singh (CI); J. Satterfield, L. Westerberg (SC).

References


Emergency Administration of Abciximab for Treatment of Patients With Acute Ischemic Stroke: Results of a Randomized Phase 2 Trial
Abciximab Emergent Stroke Treatment Trial (AbESTT) Investigators

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