Combined Approach to Lysis Utilizing Eptifibatide and Recombinant Tissue-Type Plasminogen Activator in Acute Ischemic Stroke-Full Dose Regimen Stroke Trial

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Background and Purpose—The Combined Approach to Lysis Utilizing Eptifibatide and Recombinant Tissue-Type Plasminogen Activator (r-tPA; CLEAR) in Acute Ischemic Stroke (AIS) and CLEAR-Enhanced Regimen (CLEAR-ER) trials demonstrated safety of reduced dose r-tPA plus the glycoprotein 2b/3a inhibitor, eptifibatide, in AIS compared with r-tPA alone. The objective of the CLEAR-Full Dose Regimen (CLEAR-FDR) trial was to estimate the rate of symptomatic intracerebral hemorrhage (sICH) in AIS patients treated with the combination of full-dose r-tPA plus eptifibatide.

Methods—CLEAR-FDR was a single-arm, prospective, open-label, multisite study. Patients aged 18 to 85 years treated with 0.9 mg/kg IV r-tPA within 3 hours of symptom onset were enrolled. After obtaining consent, eptifibatide (135 μg/kg bolus and 2-hour infusion at 0.75 μg/kg per minute) was administered. The primary end point was the proportion of patients who experienced sICH within 36 hours. An independent clinical monitor adjudicated if an sICH had occurred and an independent neuroradiologist reviewed all images. The stopping rule was 3 sICHs within the first 19 patients or 4 sICHs within 29 patients.

Results—From October 2013 to December 2014, 27 patients with AIS were enrolled. Median age was 73 years (range, 34–85; interquartile range, 65–80) and median National Institute of Health stroke scale score was 12 (range, 6–26; interquartile range, 9–16). One sICH (3.7%; 95% confidence interval, 0.7%–18%) was observed.

Conclusions—These results demonstrate comparable safety of full-dose r-tPA plus eptifibatide with historical rates of sICH with r-tPA alone and support proceeding with a phase 3 trial evaluating full-dose r-tPA combined with eptifibatide to improve outcomes after AIS. (Stroke. 2015;46:2529-2533. DOI: 10.1161/STROKEAHA.115.010260.)

Key Words: clinical trial ■ eptifibatide ■ stroke ■ tissue-type plasminogen activator

Intravenous recombinant tissue-type plasminogen activator (r-tPA) remains the only proven medical therapy for improving functional outcomes after acute ischemic stroke (AIS). Unfortunately, r-tPA alone is often inadequate for opening occluded intracranial arteries with recanalization of large arterial occlusions in only ≈50% with subsequent reocclusion of 14% to 34% of initially recanalized arteries.1-4 Recent trials of endovascular therapy found that carefully selected patients treated with endovascular and intravenous r-tPA have improved outcomes compared with r-tPA alone,5-11 but half of all r-tPA treated patients do not have a proximal arterial occlusion.12 Furthermore, access of patients with stroke to centers capable of delivering endovascular therapy is limited.13 Thus, intravenous medical treatments that augment reperfusion and improve functional outcomes beyond that seen with r-tPA alone remain sorely needed.

We have previously conducted 2 randomized phase 2 clinical trials of escalating doses of intravenous r-tPA plus intravenous eptifibatide, a platelet glycoprotein 2b/3a inhibitor that prevents platelet aggregation,14 versus r-tPA alone in AIS patients treated with r-tPA within 3 hours of symptom onset. The 94-patient Combined Approach to Lysis Utilizing Eptifibatide and Recombinant Tissue-Type Plasminogen Activator (CLEAR) stroke trial randomized patients with AIS to low-dose r-tPA (tier 1, 0.3 mg/kg and tier 2, 0.45 mg/kg) plus eptifibatide (75 μg/kg bolus followed by 0.75 μg/kg per minute).
minute infusion for 2 hours) or standard-dose r-tPA (0.9 mg/kg). The symptomatic intracerebral hemorrhage (sICH) rate in the combination arm was 1.4% and there was no signal of improved efficacy for r-tPA alone. The follow-up 126-patient CLEAR-Enhanced Regimen (CLEAR-ER) trial found that a slightly higher dose of r-tPA (0.6 mg/kg) plus a higher eptifibatide bolus (135 µg/kg) followed by the 2-hour infusion at 0.75 µg/kg per minute had an sICH rate of 2% (95% confidence interval [CI], 0.5%–6.9%) and a direction of effect in favor of the combination therapy for intravenous r-tPA with a nonsignificant, unadjusted increase in the proportion of patients with modified Rankin scale (mRS) scores of 0 to 1 or return to baseline of 13.5% (95% CI, −7.7% to 34.7%).

Given the safety of reduced dose r-tPA combined with eptifibatide, the primary objective of the CLEAR-Full Dose Regimen (CLEAR-FDR) Stroke Trial was to estimate the rate of sICH, as defined in the National Institutes of Neurological Disorders and Stroke (NINDS) r-tPA Stroke Trials, in AIS patients treated with the combination of full-dose r-tPA (0.9 mg/kg) plus eptifibatide when r-tPA is initiated within 3 hours of symptom onset. We hypothesized that the sICH rate would be <8%. An evaluation of the safety of the full-dose combination therapy is required before proceeding with a phase 3 trial.

Methods
This was a single-arm, prospective, open-label, 8-site study within a single metropolitan area served by 1 stroke team. The primary outcome was the proportion of patients who experienced sICH as defined in the NINDS r-tPA Stroke Trials within 36 hours of r-tPA initiation. An independent neuroradiologist reviewed all images and determined if any hemorrhage was present. All cases for which a hemorrhage occurred were then reviewed by an independent clinical monitor who classified the hemorrhage as symptomatic or not using the NINDS r-tPA trial definition. Secondary outcomes included the proportion of patients who developed parenchymal hemorrhage types 1 and 2, serious systemic bleeding (defined as requiring transfusion of ≥3 units of blood), and 90-day outcomes as measured by the mRS. Ninety-day mRS was determined by in-person or phone interview with the patient or surrogate using validated methods. Institutional Review Board (IRB) approval was obtained for all participating sites and no study procedures occurred before IRB and hospital approval. Key inclusion and exclusion criteria beyond eligibility for intravenous r-tPA are shown in Table 1.

Interventions
After 0.9 mg/kg IV r-tPA was started in eligible patients with ischemic stroke per standard of care, the patient or surrogate was approached for participation in the study and consent obtained in eligible patients. Open label eptifibatide (bolus 135 µg/kg and 2-hour infusion at 0.75 µg/kg per minute) was started as soon as possible after consent was obtained. The goal was to start eptifibatide within 40 minutes of initiation of r-tPA. A repeat NIH stroke scale was performed at the end of the 2-hour eptifibatide infusion and at 24 (±6) hours after initiation of r-tPA.

Stopping Rules
The primary goal was to ensure with high probability, which we defined as 80%, that the rate of sICH did not exceed 8%. The 8% expected sICH rate was based on the observed rate in NINDS r-tPA trial patients with baseline National Institute of Health stroke scale score (NIHSS) ≥6. The stopping rule was 3 sICH cases within the first 19 patients enrolled or 4 sICH cases within 29 patients enrolled. Assuming the sICH rate was 8% then the probability of observing ≥3 events of 19, or ≥4 events of 29, would be <20%. If the study was stopped because of observing ≥3 events of 19 or 4 events of 29, then the hypothesis that the sICH rate is <8% would be rejected. Otherwise, it would be accepted. The probability was computed assuming the binomial distribution with a mean of 0.08 for sICH rate. We planned to enroll ≤30 patients as long as there was at least an 80% probability that the sICH rate was no >8% given the observed data. The study is registered at clinicaltrials.gov (NCT01977456).

Results
From October 2013 to December 2014, we enrolled 27 patients. The study was stopped after 27 enrollments because of the fact that the primary safety threshold had been crossed. With only 1 sICH of 27, 4 sICHs of 29 is impossible. Figure 1 shows screening and eligibility data. Patient characteristics are shown in Table 2. The median age for enrolled patients was 73 years (range, 34–85; interquartile range, 65–80). Median NIHSS for all patients was 12 (range, 6–26; interquartile range, 9–16).

The primary outcome of sICH was observed in 1 of 27 patients (3.7%; 95% CI, 0.7%–18%). Figure 2 shows the independent monitor adjudicated sICH. The prespecified secondary outcomes included rates of parenchymal hemorrhage type 1 (n=1, 3.7%) at 24 hours and parenchymal hemorrhage type 2 (n=0, 0%). Serious systemic bleeding occurred in 1 patient (3.7%). Table 3 shows the mRS distribution at 90 days for all patients. Of all enrolled patients, 17 (63%; 95% CI, 44%–78%) had an mRS score of 0 to 1 or return to prestroke function at 90 days; 12 (44%; 95% CI, 28%–63%) had score of mRS 0 to 1, 13 (48%; 95% CI, 31%–66%) had mRS score of 0 to 2, and 5 (19%; 95% CI, 8%–37%) were dead at 90 days. mRS assessments were done in-person for 24 subjects

### Table 1. Key Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects must have had a serious measurable neurological deficit on the NIH Stroke Scale because of focal brain ischemia</td>
<td>Ages ≤18 or ≥86 years</td>
</tr>
<tr>
<td>An NIH Stroke Scale score ≥5 at the time the r-tPA was begun</td>
<td>Clinical presentation suggested a subarachnoid hemorrhage, even if initial CT scan was normal</td>
</tr>
<tr>
<td>Age: 18 through 85 y (ie, candidates must have had their 18th birthday, but not had their 86th birthday)</td>
<td>Hypertension at time of treatment; systolic BP &gt;185 or diastolic &gt;110 mmHg or aggressive measures (requirement for AND repeated titrations of a continuous infusion medication) to lower blood pressure to below these limits were needed</td>
</tr>
<tr>
<td>Intravenous r-tPA therapy must have been initiated within 3 h of onset of stroke symptoms</td>
<td>Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR &gt;1.7</td>
</tr>
<tr>
<td>Ongoing renal dialysis, regardless of creatinine. Informed consent was not or could not be obtained.</td>
<td>Baseline laboratory values: positive urine pregnancy test, glucose &lt;50 or &gt;400 mg/dL, platelets &lt;100 000/mm³, Hct &lt;25%, or creatinine &gt;4 mg/dL</td>
</tr>
</tbody>
</table>

### Table 2. Patient Characteristics

- Median age for enrolled patients was 73 years (range, 34–85; interquartile range, 65–80).
- Median NIHSS for all patients was 12 (range, 6–26; interquartile range, 9–16).
and by phone for 3. At 2 and 24 hours, the median NIHSS for all enrolled patients was 8 (0–25) and 5 (0–24), respectively.

Of the 19 patients with a prestroke mRS score of 0 to 2, median age (range) was 67.5 years (34.0–85.7) and median NIHSS (range) was 11 (6–22). Of the 8 patients with a prestroke mRS score of 3 or 4, median age (range) was 75.9 years (69.1–84.8) and median NIHSS (range) was 13 (7–26).

Among patients with a prestroke mRS score of 0 to 2 (n=19), 13 (68%) had mRS score 0 to 2 at 90 days. Among patients with prestroke mRS score of 3 or 4 (n=8), 5 (62.5%) had mRS score of 3 or 4 at 90 days. The analyses by prestroke mRS were performed based on observed data and not prespecified.

A summary of the CLEAR, CLEAR-ER, and CLEAR-FDR trials is shown in Table 4.

**Table 2. Patient Characteristics (n=27)**

<table>
<thead>
<tr>
<th>Age, median (range)</th>
<th>73.4 (34.0–85.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Baseline NIHSS, median (range)</td>
<td>12 (6–26)</td>
</tr>
<tr>
<td>Prestroke mRS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17 (63)</td>
</tr>
<tr>
<td>1</td>
<td>1 (4)</td>
</tr>
<tr>
<td>2</td>
<td>1 (4)</td>
</tr>
<tr>
<td>3</td>
<td>7 (26)</td>
</tr>
<tr>
<td>4</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Time from stroke onset to IV r-tPA (min), median (range)</td>
<td>118 (71–182)</td>
</tr>
<tr>
<td>Time from start of IV r-tPA to start of eptifibatide (min), median (range)</td>
<td>37 (15–57)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (74)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (41)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>7 (26)</td>
</tr>
</tbody>
</table>

Data presented as median (minimum, maximum) or n (%). IV indicates intravenous; mRS, modified Rankin score; NIHSS, National Institute of Health stroke scale score; and r-tPA, recombinant tissue-type plasminogen activator.

**Discussion**

Our findings support the hypothesis that combining eptifibatide in the dose studied with full-dose intravenous r-tPA administered within 3 hours of symptom onset in patients with AIS is associated with an sICH rate of <8%. This represents the culmination of 3 phase 2 clinical trials conducted during an 11-year span and combining gradually increasing doses of r-tPA and eptifibatide to estimate the safety of this combination before proceeding with an efficacy trial. In all, 247 patients with ischemic stroke have been enrolled in prospective trials is shown in Table 4.

**Table 3. Ninety-Day mRS Scores**

<table>
<thead>
<tr>
<th>90-day mRS</th>
<th>(n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9 (33%)</td>
</tr>
<tr>
<td>1</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>2</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>3</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>4</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>5</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>6</td>
<td>5 (19%)</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin score.
clinical trials studying the combination of r-tPA plus eptifibatide by our group.16,17 Given the potential treatment effect observed in the previously published double-blind randomized CLEAR-ER stroke trial,17 the results of the CLEAR-FDR trial provide justification for the safety of proceeding with a phase 3 trial evaluating 0.9 mg/kg of intravenous r-tPA combined with eptifibatide to improve outcomes after AIS.

Of 27 AIS patients with a median age of 73 years and median NIHSS of 12 treated with full-dose r-tPA plus eptifibatide, we observed 1 case of sICH (Figure 1). The age, severity, and observed sICH rate are similar to those of the 101 patients treated with the combination of 0.6 mg/kg of r-tPA and the same dose of eptifibatide in CLEAR-ER.17 Notably, 30% of patients enrolled in CLEAR-FDR had a prestroke mRS score of ≥2. As such, our estimate of the safety of the combination accounts for inclusion of patients with poor prestroke function who may end up receiving the treatment in routine clinical practice should it be proven effective in a larger clinical trial.

Given the single-arm design, CLEAR-FDR was not intended to evaluate the impact of the trial intervention on functional outcomes. We note that 63% (95% CI, 44%–78%) of all enrolled patients had mRS score of 0 to 1 or return to prestroke function at 90 days but this must be taken with caution given broad CIs around this point estimate. Because about one third of enrolled patients had a prestroke mRS score of ≥1 (Table 1), a dichotomized mRS score of 0 to 1 is inadequate for evaluation of potential efficacy.

We acknowledge limitations, including the small sample size, single-arm nonblinded design, lack of vascular imaging and data on large vessel occlusion, and enrollment by a single regional stroke team. However, the primary objective of the trial was to estimate the sICH rate in AIS patients with moderate to severe stroke who were treated with the combination.

Strengths of the study include the inclusion of patients with prestroke disability who would end up receiving any proven intervention in the real world of acute stroke care, use of the standard dose of r-tPA, which would allow ready translation to a larger trial, and a sensitive definition of sICH, the NINDS r-tPA trial definition, which ensures the estimation of safety is not based on an overly restrictive definition of sICH.

We conclude that full-dose r-tPA combined with eptifibatide at the dose studied is sufficiently safe to proceed with a phase 3 trial evaluating the combination for improving outcomes in otherwise eligible patients with AIS. Before such a trial, we plan to investigate the dose–response of r-tPA plus eptifibatide via a pooled analyses of all 3 completed trials, as well as a comparison of outcomes between CLEAR-FDR patients and contemporaneously enrolled intravenous r-tPA only patients in other trials matched on important baseline demographic and clinical characteristics.

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Disclosures
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References


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