Twenty years after completion of the National Institute of Neurological Disorders and Stroke recombinant tissue-type plasminogen activator (r-tPA) stroke trial, intravenous r-tPA remains the only proven therapy for acute ischemic stroke (AIS). The recently completed 126-patient phase II Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke-Enhanced Regimen (CLEAR-ER) trial found that the addition of eptifibatide, a platelet glycoprotein 2b/3a inhibitor that prevents platelet aggregation, to intravenous r-tPA had a safety profile and direction of effect in favor of the combination therapy over intravenous r-tPA. Although this direction of effect persisted after statistical adjustment, there were baseline imbalances in the trial in favor of the combination arm with regard to age and baseline National Institutes of Health Stroke Scale (NIHSS) Score. In this article, we compared combination therapy patients from CLEAR-ER to contemporaneously enrolled intravenous r-tPA arm patients in the phase III Interventional Management of Stroke (IMS) III and Albumin in Acute Stroke (ALIAS) Part 2 trials. We compared outcome using severity-adjusted modified Rankin score (mRS) dichotomization based on baseline NIHSS Score. Secondary outcomes were mRS dichotomization as excellent (mRS, 0–1); mRS dichotomization as favorable (mRS, 0–2); and nonparametric analysis of the ordinal mRS.

**Background and Purpose**—The Combined Approach to Lysis Utilizing Eptifibatide and r-tPA in Acute Ischemic Stroke-Enhanced Regimen (CLEAR-ER) trial demonstrated safety of recombinant tissue-type plasminogen activator (r-tPA) plus eptifibatide in acute ischemic stroke (AIS). CLEAR-ER randomized AIS patients (5:1) to 0.6 mg/kg r-tPA plus eptifibatide versus standard r-tPA (0.9 mg/kg). Interventional Management of Stroke III randomized AIS patients to r-tPA plus endovascular therapy versus standard r-tPA. Albumin in Acute Stroke Part 2 randomized patients to albumin+r-tPA versus saline+r-tPA. Our aim was to compare outcomes in CLEAR-ER combination arm patients to propensity score-matched r-tPA only subjects in Albumin in Acute Stroke Part 2 and Interventional Management of Stroke III.

**Methods**—The primary outcome was 90-day severity-adjusted modified Rankin score (mRS) dichotomization based on baseline National Institutes of Health Stroke Scale. Secondary outcomes were 90-day mRS dichotomization as excellent (mRS, 0–1); mRS dichotomization as favorable (mRS, 0–2); and nonparametric analysis of the ordinal mRS.

**Results**—Eighty-five combination arm CLEAR-ER subjects were matched with 169 Albumin in Acute Stroke Part 2 and Interventional Management of Stroke III trials’ r-tPA only patients (controls). Median age in CLEAR-ER and control subjects was 68 years; median NIHSS Score in the CLEAR-ER subjects was 11 and in control subjects 12. At 90 days, CLEAR-ER subjects had a nonsignificantly greater proportion of patients with favorable outcomes (45% versus 36%; unadjusted relative risks, 1.24; 95% confidence intervals, 0.91–1.69; P=0.18). Secondary outcomes were 52% versus 34% excellent outcomes (relative risks, 1.51; 95% confidence intervals, 1.13–2.02; P=0.007); 60% versus 53% favorable outcome (relative risks, 1.13; 95% confidence intervals, 0.90–1.41; P=0.31); and ordinal Cochran–Mantel–Haenszel P=0.10.

**Conclusion**—r-tPA plus eptifibatide showed a favorable direction of effect that was consistent across multiple approaches for AIS outcome evaluation. A phase III trial to establish the efficacy of r-tPA plus eptifibatide for improving AIS outcomes is warranted. (Stroke. 2015;46:461-464. DOI: 10.1161/STROKEAHA.114.006743.)

**Key Words:** clinical trial ▪ eptifibatide ▪ tissue-type plasminogen activator
4 approaches variably proposed as optimal for acute stroke clinical trials.5–9

Methods
This was a post hoc propensity-matched analysis of data from 3 previously published randomized clinical trials. The CLEAR-ER trial was a multicenter, double-blind, randomized safety study. AIS patients treated with intravenous r-tPA within 3 hours of symptom onset were randomized to 0.6 mg/kg r-tPA plus epifibatide (135 mcg/kg bolus and a 2-hour infusion at 0.75 mcg/kg per minute; combination arm, n=101) versus standard r-tPA (0.9 mg/kg; n=25).10 The IMS III trial was a multicenter multinational randomized clinical trial of intravenous r-tPA plus endovascular therapy (n=434) versus intravenous r-tPA (n=222) in AIS patients treated with standard dose intravenous r-tPA within 3 hours of symptom onset.1 The ALIAS Part 2 trial was a multicenter multinational randomized clinical trial of albumin versus saline (n=422) versus saline patients in ALIAS Part 2, 361 received intravenous r-tPA and leaving 213 subjects available for propensity matching. Of the 419 missing, 4 with baseline mRS >1, and 4 with missing 90-day mRS), 9 subjects were excluded (1 with baseline NIHSS >14).5 Secondary outcomes included 90-day mRS dichotomization as excellent (mRS, 0–1); mRS dichotomization as favorable (mRS, 0–2); an analysis of the ordinal mRS; and NIHSS of 0 or 1 at 24 hours.

Relative risks (RR) were determined for the dichotomized efficacy outcome variables. Adjusted models included age, baseline NIHSS, and time to intravenous r-tPA using Zou modified Poisson approach.14 The nonparametric analysis of the ordinal mRS was performed using the Van Eltren form of the Cochran–Mantel–Haenszel test using the full range of the mRS as a 6-category polychotomous outcome (collapsing mRS scores of 5 with 6).15 Differences in proportions of favorable outcomes were also calculated with 95% confidence intervals (CI).

Results
Eighty-five combination arm CLEAR-ER subjects were matched with 169 ALIAS Part 2 and IMS III r-tPA only patients (62 IMS III and 107 ALIAS). Patient characteristics and propensity matching factors are presented in Table 1. Note that 18 of 107 r-tPA patients in ALIAS Part 2 also had endovascular therapy. At 90 days, CLEAR-ER subjects had a greater proportion of patients with favorable outcomes (45% versus 36%; unadjusted RR, 1.24; 95% CI, 0.91–1.69; P=0.18). Secondary outcomes were 52% versus 34% excellent outcomes (RR, 1.51; 95% CI, 1.13–2.02; P=0.007); 60% versus 53% favorable outcome (RR, 1.13; 95% CI, 0.90–1.41; P=0.31); and a shift (Cochran–Mantel–Haenszel P=0.10). At 24 hours, 20% of CLEAR-ER subjects had NIHSS 0 or 1 versus 14% of controls; difference in proportions 6% (−4%, 16%; P=0.19). Table 2 shows the adjusted and unadjusted RR and outcomes at 90 days. Table 3 shows the differences in proportions of 90-day outcomes with 95% CI. Symptomatic

### Table 1. Patient Characteristics and Propensity Matching Factors

<table>
<thead>
<tr>
<th></th>
<th>CLEAR-ER Combination Arm (n=85)</th>
<th>Control r-tPA Only (n=169)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>68 (33–86)</td>
<td>68 (31–84)</td>
<td>0.93</td>
</tr>
<tr>
<td>Male</td>
<td>42 (49%)</td>
<td>83 (49%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Black</td>
<td>11 (13%)</td>
<td>22 (13%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Baseline NIHSS, median (range)</td>
<td>11 (6–31)</td>
<td>12 (6–30)</td>
<td>0.99</td>
</tr>
<tr>
<td>Baseline mRS</td>
<td></td>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>0</td>
<td>74 (87%)</td>
<td>149 (88%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11 (13%)</td>
<td>20 (12%)</td>
<td></td>
</tr>
<tr>
<td>Time from stroke onset to intravenous r-tPA, median (range)</td>
<td>113 (54–187)</td>
<td>119 (45–240)</td>
<td>0.76</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>27 (32%)</td>
<td>38 (22%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>71 (84%)</td>
<td>123 (73%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>26 (31%)</td>
<td>40 (24%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6 (7%)</td>
<td>17 (10%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>12 (14%)</td>
<td>19 (11%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>37 (44%)</td>
<td>89 (53%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>10 (12%)</td>
<td>29 (17%)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

CLEAR-ER indicates Combined Approach to Lysis Utilizing Epifibatide and r-tPA in Acute Ischemic Stroke-Enhanced Regimen; mRS, modified Rankin score; NIHSS, National Institutes of Health Stroke Scale; and r-tPA, recombinant tissue-type plasminogen activator.
intracranial hemorrhage rates within 36 hours were 0 (0%; 95% CI, 0–4%) in CLEAR-ER subjects and 5 (3%; 95% CI, 1–7%) in r-tPA subjects. The mRS distributions for the Cochran–Mantel–Haenszel test are shown in the Figure.

On the basis of observed data for the sliding dichotomy outcome measure, the study sample size of 85 in the treatment group and 169 in the control group would achieve 80% power to detect a difference between group proportions of patients with favorable outcome of 0.18, assuming the proportion in the control group is 0.36, using a 2-sized Z test with a 0.05 significance level. Furthermore, if we assume the observed group difference in proportion of patients with favorable outcome of 0.09 (45% treatment and 36% control) is the minimum value worth detecting in future studies, a sample size of 466 in each group would achieve 80% power to detect this difference using a 2-sized Z test with pooled variance at a 0.05 significance level.

Discussion

In this post hoc analysis, we found a direction of effect in favor of the combination of r-tPA plus eptifibatide over r-tPA alone in AIS. These findings support a phase III trial to establish the efficacy of r-tPA plus eptifibatide for improving AIS outcomes.

Although sliding dichotomous or ordinal approaches have been preferentially recommended for evaluating mRS outcomes in stroke trials, we found that of the 4 approaches analyzed, dichotomization at excellent outcomes (mRS, 0–1) demonstrated the only statistically significant finding in favor of r-tPA plus eptifibatide when compared with r-tPA. A possible explanation is that for interventions within the early time window studied, dichotomizing at mRS 0 to 1 may represent a reasonable transition point between favorable and nonfavorable outcomes. Both positive trials of r-tPA in AIS showed benefit with mRS dichotomized at 0 to 1. However, given that the ECASS II trial showed no treatment effect with dichotomization at mRS 0 to 1 but was positive with mRS 0 to 2, caution must be taken in interpreting our results and full consideration given to all approaches in selecting an analysis plan for the primary outcome in a planned phase III trial.

Compared with dichotomized favorable outcomes (mRS, 0–2), our selected primary outcome, the severity-adjusted dichotomy approach (also referred to as sliding dichotomy or responder analysis) showed a slightly stronger trend in favor of the r-tPA plus eptifibatide group over r-tPA only. The ordinal analysis showed a similar trend as the sliding dichotomy in favor of the r-tPA plus eptifibatide group compared with r-tPA. As such, despite the seemingly stronger signal of efficacy shown by dichotomization at mRS 0 or 1 in this analysis, we favor the sliding dichotomy or ordinal approach for a future trial because there is no reliable way to predict the distribution of patients who would be enrolled in such a trial. Thus, if patients with more severe strokes are enrolled, dichotomizing at mRS 1 may fail to show a treatment effect as was observed in ECASS II.

In addition to the inherent limitations of an unplanned post hoc analysis, limitations of this report include the small number of available r-tPA plus eptifibatide patients for analysis. Vascular imaging was not required for CLEAR-ER and the effect of combining eptifibatide with r-tPA on the insufficient arterial recanalization rates observed with r-tPA alone remains unknown. However, the favorable direction of effect observed with r-tPA plus eptifibatide remained with comparison groups similar in age and baseline NIHSS (Table 1) and a direction of effect in favor of early improvement with the combination group based on 24-hour NIHSS of 0 or 1.

We also performed analyses using the entire data set from both ALIAS Part 2 and IMS III trials, (ie, including patients who received albumin or endovascular therapy) and the results were similar with point estimates more favorable than the results presented in this article (data not shown). Exclusion of the 18 ALIAS Part 2 patients (leaving 151 r-tPA controls) also did not change our point estimates meaningfully (data not shown).

We conclude that r-tPA plus eptifibatide showed a direction of effect that was consistent across multiple approaches for outcome evaluation in AIS. A phase III trial to establish the efficacy of r-tPA plus eptifibatide for improving AIS outcomes is warranted.

Acknowledgments

We thank Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke-Enhanced Regimen, Albumin in

<table>
<thead>
<tr>
<th>Table 3. Ninety-Day Differences in Outcome Proportions</th>
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<tbody>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>90-day mRS, sliding dichotomy</td>
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<tr>
<td>90-day mRS, 0–1</td>
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<tr>
<td>90-day mRS, 0–2</td>
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</table>

CLEAR-ER indicates Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke-Enhanced Regimen; and mRS, modified Rankin score.
Figure. mRS Distributions. ALIAS indicates Albumin in Acute Stroke; CLEAR-ER, Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke-Enhanced Regimen; IMS III, Interventional Management of Stroke; and mRS, modified Rankin score.


Sources of Funding
National Institutes of Health grants (P50 NS044283, U01NS052220, U01NS054630, and U01NS077304) and by Genentech, EkoSonic Endovascular—EKOS Corporation, Concentric Medical, Cordis Neurovascular, and Boehringer Ingelheim.

Disclosures
Dr Adeoye received significant research support from Genentech. Dr Khatri’s Department of Neurology receives payment for her research roles from Genentech (PRISMS Trial PI), THERAPY (THERAPY Trial Neurology PI), and Biogen (DSMB member). Dr Palesch received honorarium for serving as a statistical member of the Data and Safety Monitoring Committees from Biogen Idec, Inc, andBrainsgate, Ltd. Dr Broderick is awarded research monies to Department of Neurology for acute ischemic stroke-enhanced regimen stroke trial.

References
Recombinant Tissue-Type Plasminogen Activator Plus Eptifibatide Versus Recombinant Tissue-Type Plasminogen Activator Alone in Acute Ischemic Stroke: Propensity Score-Matched Post Hoc Analysis

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for The CLEAR-ER, IMS III, and ALIAS Part 2 Investigators

*Stroke*. 2015;46:461-464; originally published online December 18, 2014;
doi: 10.1161/STROKEAHA.114.006743

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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急性虚血性脳卒中における遺伝子組換え組織プラスミノーゲン活性化因子（rt-PA）＋Eptifibatide併用療法とrt-PA単独療法の比較
傾向スコアをマッチさせた事後解析

Recombinant Tissue-Type Plasminogen Activator Plus Eptifibatide Versus Recombinant Tissue-Type Plasminogen Activator Alone in Acute Ischemic Stroke
Propensity Score-Matched Post Hoc Analysis

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Abstract

背景および目的：Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Strok Enhanced Regimen（CLEAR-ER）試験では、急性虚血性脳卒中(AIS)患者における遺伝子組換え組織プラスミノーゲン活性化因子（rt-PA）＋eptifibatide併用療法の安全性が示された。CLEAR-ER試験ではAIS患者を5:1の割合でrt-PA（0.6 mg/kg）＋eptifibatide併用療法群と標準的なrt-PA単独療法群に無作為に割り付けた。Interventional Management of Stroke III（IMS III）試験では、AIS患者をrt-PA＋血管内治療群と標準的なrt-PA単独療法群に無作為に割り付けた。Albumin in Acute Stroke Part 2（ALIAS Part 2）試験では、患者をアルピミン±rt-PA群と生理食塩水±rt-PA群に無作為に割り付けた。本研究は、CLEAR-ERの併用療法群と傾向スコアをマッチさせたALIAS Part 2試験およびIMS III試験のrt-PA単独療法群の転帰を比較することを目的とした。

方法：本研究の主要評価項目は、90日の重症度で調整した変換Rankinスケール（mRS）であり、米国国立衛生研究所脳卒中スケール（National Institutes of Health Stroke Scale：NIHSS）の追跡開始時の平均値に基づいて2値化し、副次評価項目は、90日のmRSの2値化で極めて良好（mRS = 0～1）、良好（mRS = 0～2）、およびmRS序数のノンパラメトリック解析とした。

結果：CLEAR-ER試験の併用療法群（CLEAR-ER群）85例をALIAS Part 2試験およびIMS III試験のrt-PA単独療法群（対照群）169例とマッチさせた。CLEAR-ER群および対照群の年齢の中央値は68歳で、NIHSSの中央値はCLEAR-ER群で11、対照群で12であった。90日時点ではCLEAR-ER群において転帰良好の割合が多かったが、有意ではなくかった（45%対36%、未調整相対リスク = 1.24、95%信頼区間：0.91～1.69、p = 0.18）。副次評価項目では、極めて良好な転帰が52%対34%（相対リスク = 1.51、95%CI：1.13～2.02、p = 0.007）、転帰良好が60%対53%（相対リスク = 1.13、95% CI：0.90～1.41、p = 0.31）で、mRS序数のCochran-Mantel-Haenszel検定ではp = 0.10であった。

結論：rt-PA＋Eptifibatide併用療法群は効果において良好な傾向を示し、この効果はAISの転帰評価における複数のアプローチで一貫していた。AIS患者の転帰改善に対するrt-PA＋Eptifibatide併用療法の有効性を確立するために第III相試験を行うことは妥当である。