Timing of Recanalization After Intravenous Thrombolysis and Functional Outcomes After Acute Ischemic Stroke

Leonard L. Yeo, MBBS, MRCP; Prakash Paliwal, MBBS, MRCP; Hock L. Teoh, MBChB, MRCP; Raymond C. Seet, MBBS, MRCP; Bernard F. L. Chan, MBChB, MRCP; Shen Liang, PhD; Narayanaswamy Venketasubramanian, MBBS, MRCP; Rahul Rathakrishnan, MD, MRCP; Aftab Ahmad, MBBS, MRCP; Kay W. P. Ng, MBBS, MRCP; Pei K. Loh, MBBS, MRCP; Jonathan J. Y. Ong, MBBS, MRCP; Benjamin R. Wakerley, MD, PhD; Vincent F. Chong, MBBS, FRCR; Girish Bathla, MD, FRCR; Vijay K. Sharma, MBBS, MRCP

**Background:** Recanalization of occluded intracranial arteries remains the aim of intravenous (IV) tissue plasminogen activator (tPA) therapy in acute ischemic stroke (AIS).

**Objective:** To examine the timing and impact of recanalization on functional outcomes in AIS.

**Design:** A longitudinal cohort of consecutive IV tPA–treated patients with AIS from January 2007 through December 2010. Data were collected for demography, risk factors, stroke subtypes, blood pressure, and National Institutes of Health Stroke Scale scores. Early recanalization (ER) was identified by transcranial Doppler monitoring during the first 2 hours of treatment. Recanalization was reevaluated at 24 hours by computed tomographic angiography (CTA). Patients with ER and patent index artery at 24 hours on CTA were labeled as having persistent recanalization (PR). Recanalization at 24 hours on CTA regardless of transcranial Doppler status was labeled as CTR. Favorable outcome was defined as a modified Rankin Scale score of 0 to 1 at 3 months.

**Setting:** University hospital stroke center.

**Patients:** A total of 240 patients with AIS who underwent IV tPA treatment.

**Results:** Of 2238 patients with AIS, 240 (11%) received IV tPA. The median age was 65 years (range, 19-92 years) and 44% of the study group was male. The median National Institutes of Health Stroke Scale score was 17 (range, 3-35) and the median onset-to-treatment time was 149 minutes (range, 46-270 minutes). Of the 240 patients, 122 (50.8%) achieved favorable outcomes at 3 months. Data for ER, PR, and CTR were analyzed for 160 patients. Early recanalization was seen in 82 patients (51.3%); 67 cases (81.7%) had PR and 84 cases (52.5%) had CTR. National Institutes of Health Stroke Scale score at onset (odds ratio per 1-point increase, 0.938; 95% CI, 0.888-0.991), ER (odds ratio, 3.048; 95% CI, 1.537-6.046), PR (odds ratio, 6.046; 95% CI, 2.382-12.464), and CTR (odds ratio, 4.329; 95% CI, 2.131-8.794) were independent predictors of favorable outcomes.

**Conclusions:** Intravenous tPA–induced arterial recanalization within the first 24 hours in AIS is a strong predictor of favorable outcomes at 3 months.


©2013 American Medical Association. All rights reserved.

---

NTRAVENOUS (IV) TISSUE PLASMINOGEN ACTIVATOR (tPA) remains the only approved therapeutic agent for arterial recanalization in acute ischemic stroke (AIS). Although recanalization of the acutely occluded intracranial artery remains the major aim of IV tPA therapy in patients with AIS, to our knowledge, the relationship between arterial recanalization and stroke recovery has been described in only a few studies. Recent studies that have reported recanalization mostly pertain to interventional therapies or a combined IV tPA and interventional approach rather than IV tPA only. The information about early recanalization (ER) during the first 2 hours of IV tPA infusion may help physicians identify patients suitable for rescue reperfusion therapies. Some patients with ER may develop reocclusion within the first 24 hours and contribute to wide variations in the rates of favorable outcomes. Identifying patients with reocclusion or persistent arterial occlusion (PAO) may help the treating physi-
A retrospective cohort design was used to analyze the prospectively collected stroke thrombolysis registry data from consecutive patients admitted for AIS from January 2007 through December 2010. Our tertiary care center provides around-the-clock acute stroke thrombolysis service. Patients with AIS are first attended by emergency department physicians to evaluate their eligibility for intravenous thrombolysis treatment. Our comprehensive acute stroke team, consisting of a stroke neurologist, radiologist, and laboratory staff, is then activated for a fast-track evaluation. By the time the noncontrast computed tomographic (CT) scan of the brain is completed, routine laboratory examination results (full blood count, prothrombin time, blood glucose, and renal functions) are available to the treating neurologist. All patients considered eligible for IV tPA therapy undergo CT angiography (CTA) of the neck and brain, if there are no contraindications. We follow the inclusion and exclusion criteria of the National Institute of Neurological Disorders and Stroke study for selecting candidates for thrombolysis. In addition, we exclude patients with CT evidence of extensive early ischemic change (affecting more than one-third of the middle cerebral artery [MCA] territory). We use the standard dose of IV tPA (total dose of 0.9 mg/kg; maximum of 90 mg), with 10% given as an IV bolus and the remaining by continuous infusion for 3 hours.

For this study, the data collected included demographic characteristics and vascular risk factors such as the presence of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, and smoking, as well as blood pressure at hospital admission. Acute ischemic stroke was classified into various subtypes using the Trial of Org in Acute Stroke Treatment classification, based on the etiopathologic mechanisms. Accordingly, AIS was categorized as large artery atherosclerosis, cardioembolism, small vessel occlusion, stroke of other determined etiology, or stroke of undetermined etiology. National Institute of Health Stroke Scale (NIHSS) scores were recorded for all the cases by certified neurologists before IV tPA bolus at 2 hours and 24 hours after treatment initiation.

Results showed that the average age of the patients was 65 years (range, 19-92 years), 44% were male, and the median NIHSS score was 17 (range, 3-35). Hypertension was the most prevalent vascular risk factor, seen in 181 patients (75%), followed by hypercholesterolemia in 137 patients (57%), atrial fibrillation in 85 (35%), diabetes mellitus in 70 (29%), and smoking in 62 (26%). Cardioembolism, seen in 106 patients (44%), was the most common stroke subtype in our study cohort followed by large artery atherosclerosis in 72 cases (30%) (Table 1).

Of the 2238 patients with AIS admitted to our institution during the study, 240 (11%) received IV tPA therapy within 4.5 hours of symptom onset. The various demographic characteristics, vascular risk factors, and stroke subtypes are shown in Table 1. Briefly, the median age was 65 years (range, 19-92 years), 44% were male, and the median NIHSS score was 17 (range, 3-35). Hypertension was the most prevalent vascular risk factor, seen in 181 patients (75%), followed by hypercholesterolemia in 137 patients (57%), atrial fibrillation in 85 (35%), diabetes mellitus in 70 (29%), and smoking in 62 (26%). Cardioembolism, seen in 106 patients (44%), was the most common stroke subtype in our study cohort followed by large artery atherosclerosis in 72 cases (30%) (Table 1).

On the pretreatment CTA, MCA was the most common site of intracranial arterial occlusion, seen in 126 patients (52.5%; 110 in M1 MCA and 16 in M2 MCA). Acute occlusion of the terminal internal carotid artery was noted in 49 patients (20.4%), while 26 patients (10.8%) had vertebrobasilar arterial occlusion. Tandem arterial occlusions involving the internal carotid artery were formed with a multidetector helical scanner and CT scans were obtained at a 1.3-mm slice thickness with a 1-mm interval during a bolus injection of 70 mL of contrast material. Multiplanar reformats were created in the axial, coronal, and sagittal planes.

Arterial patency was assessed at 24 hours by a repeat CTA. Patients with recanalization on TCD at 2 hours as well as on CTA at day 2 were labeled as having persistent recanalization (PR). The absence of recanalization of an occluded artery on early TCD monitoring and CTA on day 2 was called PAO. Patients with recanalization on CTA at day 2, regardless of the status on TCD at 2 hours, were analyzed as a group labeled as CTR.

The safety of IV tPA treatment was assessed by the rates of symptomatic intracerebral hemorrhage, defined as any bleeding on CT scan and an increase in NIHSS score by at least 4 points. All the patients were followed up by their primary neurologist (one who performed the initial assessment and treated the patient with IV tPA). Good functional outcomes at 3 months were defined as modified Rankin Scale (mRS) score of 0 or 1. None of our patients treated with IV tPA was lost to follow up, and there were no missing data for final analysis.

We present the numerical variables as means and standard deviations or medians and ranges. Categorical variables are presented as percentages. Numerical predictors were tested by using 2-sample t test or Mann-Whitney U test where applicable. Categorical predictors were evaluated by using χ² test or Fisher exact test where applicable. Initially, univariable analyses of potential predictors were performed. Multivariable analyses were performed with logistic regression to identify predictors of good functional outcomes at 3 months. To maximize sensitivity, those variables with a univariable association of P < .20 were included as candidates into a multivariable logistic regression model with backward stepwise selection procedure. Predictor variables that were significant at P < .05 were retained in the multivariable model. Associations are presented as odds ratios (ORs) with corresponding 95% confidence intervals. The test results for multicollinearity for recanalization on TCD and recanalization on CTA were negative (tolerance for both variables >0.5). The Statistical Package for Social Science version 20 for Windows (SPSS Inc) was used for statistical analyses.
Cardioembolic and large artery atherosclerosis groups (OR, 2.588; 95% CI, 1.7465; 95% CI, 0.8505-3.5864; \( P = .01 \)). Interestingly, 63.1% of patients with CTR also achieved good functional outcomes at 3 months.

On TCD monitoring at 2 hours, patients with cardioembolic sources were more likely to recanalize than those with large artery atherosclerosis (OR, 2.588; 95% CI, 1.7465; 95% CI, 0.8505-3.5864; \( P = .01 \)). On CTA at 24 hours, there was no significant difference in recanalization between the cardioembolic and large artery atherosclerosis groups (OR, 1.7465; 95% CI, 0.8505-3.5864; \( P = .13 \)) (eTables 1-4, http://www.jamaneuro.com).

When recanalization rates were analyzed according to the occluded vessel, we did not observe significant differences in the rates of recanalization among the M1 MCA, basilar, and carotid-T occlusions. Interestingly, the basilar artery occlusions showed a high rate of recanalization, with 10 of 19 (53%) recanalized on TCD at 2 hours, while 9 of 19 (47%) showed recanalization at 24 hours on CTA. The patients with M2 occlusions had better recanalization rates than expected. Although there were only 8 cases with tandem lesions in our study cohort, they showed poor rates of recanalization (eTables 1-4).

Factors associated with favorable outcomes at 3 months on univariable analysis were younger age, lower baseline NIHSS score, and earlier timing of treatment.
recanalization (Table 2). However, on multivariable analysis, NIHSS score at onset (OR per 1-point increase, 0.938; 95% CI, 0.888-0.991), ER compared with no recanalization on TCD (OR, 3.048; 95% CI, 1.537-6.046), and PR compared with PAO (OR, 5.449; 95% CI, 2.382-12.464) were found to be independent predictors of favorable outcomes at 3 months. The presence of CTR was also an independent predictor of good outcomes compared with no CTR (OR, 4.329; 95% CI, 2.131-8.794) (Table 3).

### Table 2. Differences in the Characteristics of Patients With Good and Poor Functional Outcomes at 3 Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
<th>mRS Scores of 0-1 (n = 75)</th>
<th>mRS Scores of 2-6 (n = 85)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>Age</td>
<td>62 (35-87)</td>
<td>71 (38-91)</td>
<td>.001</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>45 (60)</td>
<td>42 (49)</td>
<td>.18</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>51 (68)</td>
<td>60 (71)</td>
<td>.72</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>18 (24)</td>
<td>25 (29)</td>
<td>.44</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td>35 (47)</td>
<td>38 (45)</td>
<td>.74</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td>20 (27)</td>
<td>35 (41)</td>
<td>.05</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td>20 (27)</td>
<td>20 (24)</td>
<td>.58</td>
</tr>
<tr>
<td>Pre-tPA NIHSS score, median (range)</td>
<td></td>
<td>16 (4-35)</td>
<td>20 (4-30)</td>
<td>.002</td>
</tr>
<tr>
<td>Pre-tPA systolic blood pressure, median (range), mm Hg</td>
<td></td>
<td>153 (110-220)</td>
<td>158 (112-208)</td>
<td>.85</td>
</tr>
<tr>
<td>Onset-to-treatment time, median (range), min</td>
<td></td>
<td>150 (57-330)</td>
<td>150 (46-270)</td>
<td>.70</td>
</tr>
<tr>
<td>No. of patients out of 82 ER patients</td>
<td></td>
<td>50 (67)</td>
<td>32 (38)</td>
<td>.001</td>
</tr>
<tr>
<td>No. of patients out of 67 PR patients</td>
<td></td>
<td>45 (60)</td>
<td>22 (26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of patients out of 84 CTR patients</td>
<td></td>
<td>53 (63)</td>
<td>31 (36)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CTR, recanalization at 24 hours on computed tomographic angiography; ER, early recanalization; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PR, persistent recanalization; tPA, tissue plasminogen activator.

### Table 3. Relationship Between Timing of Recanalization and Functional Outcomes at 3 Months

<table>
<thead>
<tr>
<th>Analysis</th>
<th>mRS Scores of 0-1 at 3 mo</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER vs no recanalization at 2 h on TCD</td>
<td>3.048 (1.537-6.046)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>PR vs PAO</td>
<td>5.449 (2.382-12.464)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>CTR vs no recanalization at 24 h on CTA</td>
<td>4.329 (2.382-8.794)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CTA, computed tomographic angiography; CTR, recanalization at 24 hours on CTA; ER, early recanalization; mRS, modified Rankin Scale; OR, odds ratio; PAO, persistent arterial occlusion; PR, persistent recanalization; TCD, transcranial Doppler.

Although some studies have described the rates of arterial recanalization in AIS,1,12,13 to our knowledge, most of them had an interventional component and only a few of them evaluated the temporal profile of recanalization after only IV tPA therapy.14 Continuous TCD monitoring during IV tPA infusion is the best tool for bedside diagnosis of arterial recanalization within the first 2 hours of treatment initiation.14,15 Our observations regarding ER on TCD monitoring during the first 2 hours of treatment initiation in 82 patients (51.3%) are consistent with the study by Ribo et al,16 who documented recanalization rates of 53% in their cohort. Kimura et al17 used magnetic resonance angiography to detect recanalization at 1 hour after IV tPA bolus. In their study of 102 patients, magnetic resonance angiography within 1 hour after IV tPA infusion showed ER in only 42 patients (41.2%). The lower rates of ER in this study could have occurred because of the use of a lower-dose regimen (0.6 mg/kg; maximum of 60 mg) in Japan.18

It is important to note that all patients who achieve ER may not always achieve a favorable outcome. Ahmed et al19 reported that having large ischemic lesions on diffusion-weighted magnetic resonance imaging before IV tPA thrombolysis was associated with a poor outcome even if ER occurred. Furthermore, reocclusion within the first 24 hours of thrombolysis may occur in a considerable proportion of patients. Ribo et al16 described reocclusion in 4% of their study cohort at 6 hours after treatment initiation. Although we did not evaluate arterial recanalization/reocclusion at 6 hours, we observed that 15 of our patients with ER (18.3%) developed reocclusion on CTA performed on day 2. Early recanalization occurs in most patients within the first 2 hours and only a small proportion of those who do not achieve ER during this period may achieve recanalization by 6 hours (8%).20 We observed a similar trend for additional recanalization at 24 hours on CTA in 17 additional cases (21.8%).

Our study shows a higher proportion of better outcomes in patients with arterial recanalization on day 2 on CTA, regardless of the arterial patency at 2 hours after IV tPA bolus (CTR). Compared with PAO, CTR was an independent predictor of good outcomes (OR, 4.329; 95% CI, 2.131-8.794). Our findings are consistent with previous studies that demonstrated improved functional outcomes with delayed recanalization.20 In a study of 77 patients, von Kummer et al21 evaluated arterial recanalization at between 8 and 24 hours after treatment initiation. All the patients in their study who achieved

©2013 American Medical Association. All rights reserved.
delayed recanalization had good functional outcomes. Interestingly, recanalization at 24 hours increased the proportion of good outcomes from 23% to 75% in a subgroup of patients. Recanalization did not affect mortality independently in this study, but the meta-analysis by Rha and Saver\(^2\) found an association between fatal outcomes and recanalization status within 6 hours; fatal outcomes occurred in 12.1% of recanalized patients vs 41.1% of non-recanalized patients (OR, 0.22; 95% CI, 0.10-0.51). We did not observe such an association, perhaps owing to our small sample size.

Our higher rates of good functional outcomes may be attributed to the high recanalization documented both on TCD and the follow-up CTA at 24 hours. A total of 51.3% of our patients had recanalization on TCD within 2 hours, while the rate of arterial recanalization at 24 hours on CTA was 52.9%.

Higher rates of tPA-induced recanalization and improved outcomes are consistent with the observations from various reports from Asia.\(^23\) Perhaps racial differences in coagulation-fibrinolysis factors and higher proportions of cardioembolism among Asians contributed toward the higher rates of recanalization owing to the soft and fibrin-rich blood clots as well as higher plasma concentrations of fibrinogen and plasminogen activator inhibitor among white individuals than Japanese individuals.\(^22,23\)

Continuous TCD monitoring is one of the simplest methods for observing recanalization induced by IV tPA in real-time. However, TCD exposure is known to enhance the rates of arterial recanalization in acute stroke.\(^3\) A study by Molina et al\(^24\) showed that recanalization at 2 hours in 39% of the patients given IV tPA increased to 68% of patients at 2 hours if continuous TCD monitoring was used. The role of TCD in enhancing arterial recanalization appears evident from the lower recanalization rates in other studies that used different imaging modalities.\(^17\) A recent meta-analysis by Tsivgoulis et al\(^25\) demonstrated the safety and signal of efficacy with ultrasonography exposure of the clot during IV tPA thrombolysis. In our study, recanalization was observed in 51.2% of patients who underwent continuous TCD monitoring during thrombolysis. Compared with the study by Molina et al,\(^24\) the relatively lower rates of recanalization with TCD exposure at our center could be owing to the inclusion of all intracranial arterial occlusions as well as higher proportions of proximal MCA occlusions. Furthermore, compared with previous reports,\(^26-28\) we could detect intracranial occlusion in a very high proportion of patients (92%). This is probably related to the median NIHSS scores in our patient cohort, which were relatively higher in comparison to the reports from the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study (median NIHSS score, 11; vessel occlusion rate, 74%),\(^29\) the study by Sims et al\(^17\) (median NIHSS score, 14; vessel occlusion rate, 64%), and the tenecteplase trial (median NIHSS score, 14; vessel occlusion rate, 73.5%).\(^28\)

Some limitations of our study need to be acknowledged. First, we recorded arterial recanalization only within the first 2 hours of treatment initiation and at 24 hours. Information about the arterial patency between these 2 time frames is lacking. It is possible that some of the patients could have achieved recanalization soon after the first 2 hours of thrombolysis and contributed toward good functional outcomes. The functional outcomes in such cases may not be vastly different than the patients with ER. The recanalization-reocclusion-recanalization phenomenon could also have played an important role in determining the functional outcomes. Second, comparison of our findings of ER with various previous studies might be criticized owing to the variable definition of ER. While we used recanalization status at 2 hours, Kimura et al\(^17\) used a 1-hour definition and Rha and Saver\(^2\) defined it as a composite of 6 hours and 24 hours. Another limitation is the missing data on recanalization by TCD or CTA in 61 of 221 patients; however, there were no major statistical differences between the excluded patients and the patients with TCD data at 2 hours and CTA data at 24 hours who were included (Table 1). Lastly, a considerable proportion of our patients who did not achieve recanalization during the first 2 hours of treatment could be considered eligible for further interventional therapeutic modalities. However, we did not have a neurointerventional team at our center during the study. We do not wish to convey the message that the stroke neurologist should not seek recanalization by various available interventional techniques. Every attempt should be made to achieve ER according to the best resources available to the center.

In conclusion, we reiterate that any recanalization induced by IV tPA during the first 24 hours after AIS is a strong predictor of favorable outcomes at 3 months. Although arterial patency might fluctuate during the first 24 hours after AIS, maintaining PR during this critical period results in better functional outcomes.

Accepted for Publication: August 27, 2012.
Published Online: December 10, 2012. doi:10.1001/2013.jama-neurol.547
Correspondence: Leonard L. L. Yeo, MBBS, MRCP, Division of Neurology, Department of Medicine, National University Health System, Singapore 119228 (leonard_ll_yeo@nuhs.edu.sg).

Author Contributions: Study concept and design: Yeo, Paliwal, Teoh, Seet, Chan, and Sharma. Acquisition of data: Yeo, Paliwal, Seet, Chan, Ahmad, Ng, Loh, Ong, Wakerley, and Chong. Analysis and interpretation of data: Yeo, Liang, Venketasubramanian, Rathakrishnan, Bathla, and Sharma. Drafting of the manuscript: Yeo, Teoh, Seet, Ahmad, and Wakerley. Critical revision of the manuscript for important intellectual content: Paliwal, Seet, Chan, Liang, Venketasubramanian, Rathakrishnan, Ng, Loh, Ong, Chong, Bathla, and Sharma. Statistical analysis: Yeo, Liang, and Sharma. Administrative, technical, and material support: Yeo, Paliwal, Chan, Ahmad, Ng, Loh, Ong, Wakerley, and Chong. Study supervision: Teoh, Seet, Venketasubramanian, Rathakrishnan, Bathla, and Sharma.

Conflict of Interest Disclosures: None reported.


18. Yamaguchi T, Mori E, Minematsu K, et al; Japan Alteplase Clinical Trial (J-ACT) Group. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). *Stroke*. 2006;37(7):1810-1815.


©2013 American Medical Association. All rights reserved.