Low Rates of Acute Recanalization With Intravenous Recombinant Tissue Plasminogen Activator in Ischemic Stroke
Real-World Experience and a Call for Action

Rohit Bhatia, MD, DM, DNB; Michael D. Hill, MD, FRCPC; Nandavar Shobha, DNB, DM; Bijoy Menon, MD, DM; Simerpreet Bal, MD, DM; Puneet Kochar, MD; Tim Watson, MD, FRCPC; Mayank Goyal, MD, FRCPC; Andrew M. Demchuk, MD, FRCPC

Background and Purpose—Acute rates of recanalization after intravenous (IV) recombinant tissue plasminogen activator (rt-PA) in proximal vessel occlusion have been estimated sparingly, typically using transcranial Doppler (TCD). We aimed to study acute recanalization rates of IV rt-PA in CT angiogram-proven proximal (internal carotid artery [ICA], M1 middle cerebral artery [MCA], M2-MCA, and basilar artery) occlusions and their effects on outcome.

Materials and Methods—The CT angiogram database of the Calgary stroke program was reviewed for the period 2002 to 2009. All patients with proximal vessel occlusions receiving IV rt-PA who were assessed for recanalization by TCD or angiogram (for acute endovascular treatment) were included for analysis. Rates of acute recanalization as observed on TCD/first run of angiogram and postendovascular therapy recanalization rates were noted. Modified Rankin Scale score ≤2 at 3 months was used as a good outcome.

Results—Among 1341 patients in the CT angiogram database, 388 patients with proximal occlusion were identified. Of these, 216 patients had received IV rt-PA; 127 patients underwent further imaging to assess recanalization. Among the patients undergoing TCD (n=46) and cerebral angiogram (n=103), only 27 (21.25%) patients had acute recanalization. By occlusion subtype, the rates of recanalization were: distal ICA (with or without ICA neck occlusion or stenotic disease) 1 of 24 (4.4%); M1-MCA (with or without ICA neck occlusion or stenotic disease) 21 of 65 (32.3%); M2-MCA 4 of 13 (30.8%); and basilar artery 1 of 25 (4%). Onset to rt-PA time was comparable in patients with and without recanalization. Recanalization (P<0.0001; risk ratio, 2.7; 95% confidence interval, 1.5–4.6) was the strongest predictor of outcome (adjusted for age and National Institutes of Health Stroke Scale score).

Conclusions—A low rate of acute recanalization was observed with IV rt-PA in proximal vessel occlusions identified by baseline CT angiogram. Recanalization was the strongest predictor of good outcome. (Stroke. 2010;41:2254-2258.)

Key Words: intracranial occlusion ■ ischemic stroke ■ recanalization ■ thrombolysis

Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) treatment for acute ischemic stroke1,2 works by achieving recanalization of intracranial occlusion resulting in restoration of flow and prevention of infarct expansion.3 Data on recanalization after IV thrombolysis are limited to small angiographic and transcranial Doppler (TCD) monitoring studies.4 None of the major IV thrombolysis trials has assessed the baseline occlusion status or recanalization rates after treatment. In an era when there is increasing use of endovascular therapies for recanalization, in the absence of robust evidence from randomized controlled trials, there is a desperate need for clear data on the rates of recanalization with IV rt-PA.5 The present study reports the rates of acute recanalization of proximal intracranial vessel occlusions identified by baseline CT angiography (CTA) among acute ischemic stroke patients treated with IV rt-PA.

Patients and Methods
We identified patients presenting with acute ischemic stroke secondary to major vessel occlusion from the CT Angiography database of the Calgary Stroke Program at the Foothills Medical Centre, University of Calgary, Canada. The Calgary CTA database is a Human Research and Ethics Board-approved retrospective study of patients with an acute stroke syndrome presentation who have been imaged with CTA of the extracranial and intracranial circulations. All patients had acute ischemic stroke diagnosed based on history and examination by a neurologist. The decision to perform CTA was made at the discretion...
of the treating stroke neurologist or stroke fellow; in practice, nearly all acute stroke cases undergo acute CTA at the time of the brain CT at our institution. We performed standard noncontrast CT on a multislice scanner (GE Medical Systems or Siemens, Siemens Medical Solutions) using 170 mV and 120 mAs with 5-mm slice thickness. Coverage was from skull base to vertex with continuous axial slices parallel to the orbitomeatal line. CTA was performed with a helical scan technique. We obtained acquisitions after a single bolus IV contrast injection of 90 to 120 mL of the iodinated, nonionic, hypo-osmolar XCM ioversol (Optiray-320; Mallinckrodt Medical Inc) into an antecubital vein at 3 to 5 mL/sec. Image acquisition was auto-triggered by the appearance of contrast media in the ascending aorta. Minimum coverage was from foramen magnum to centrum semiovale with 0.6-mm to 1.0-mm slice thickness.

A thorough search was made for any vascular stenosis or occlusion on the CTA. The occlusions were categorized into M1 middle cerebral artery (MCA; including tandem proximal extracranial carotid occlusions or stenosis plus M1-MCA), M2-MCA (including tandem proximal extracranial carotid occlusions or stenosis plus M2-MCA), distal internal carotid artery (ICA) terminus (T or L) type, carotid occlusion (including tandem proximal extracranial carotid occlusions or stenosis plus ICA terminus), and vertebro-basilar occlusion. In eligible patients, treatment with IV rt-PA at a dose of 0.9 mg/kg was started as soon as possible. Clinical, demographics, and risk factor profile, as well as treatment process interval times, were noted in all patients. The stroke mechanism was classified using the TOAST criteria. Patients enrolled in the International Management of Stroke III study were excluded. The data were prospectively recorded in the charts by stroke staff or clinical fellows during the hospital stay and in the clinic files on follow-up and were retrospectively extracted.

TCD was performed by experienced staff to assess the recanalization status of the occluded vessel during the rt-PA infusion. TCD was started concurrently with rt-PA administration and was performed for a maximum of 120 minutes. Standard thrombolysis in brain ischemia (TIBI) grading (TIBI 0 to 5) was used to score the vessel flow.6,7 Recanalization was defined as partial (TIBI 3, 4) or complete (TIBI 5). Among the patients undergoing cerebral angiography for endovascular revascularization (using chemical or mechanical thrombolysis either alone or in combination), the recanalization status was assessed at the initial performance of the angiogram and was graded using thrombolysis in myocardial ischemia (TIMI) grading (0 to 3). TIMI grades were classified into absent (TIMI 0–1) and partial (TIMI 2) or complete recanalization (TIMI 3). TIMI scores on TCD have been shown to have good correlation with angiographic TIMI scoring system. After endovascular treatment, the same angiographic grading was applied to assess the final degree of recanalization.

Patients were categorized by recanalization status into early after rt-PA (group 1), postendovascular treatment (group 2), and nonrecanalization (group 3). The primary outcome was recanalization defined as TIMI 2 to 3 or TIBI 3 to 5. Secondary outcomes were modified Rankin Scale score 0 to 2 and death at 90 days. Data are reported using standard descriptive statistics. We used conventional levels of significance at alpha of 0.05, and all tests were 2-tailed. A multivariable model showed that recanalization was the strongest predictor of good outcome (Table 3). The symptomatic ICH rate was 6.8%.

Discussion

Our study shows a low rate of acute recanalization with IV rt-PA in a CTA-proven occlusion cohort with severe stroke. The data also confirm an independent and strong association of recanalization (especially early) with good outcome and reduced mortality. The outcomes improved with a proximal to a distal gradient, suggesting that the burden of thrombus is important.8

In the only angiographic study of systemic thrombolysis (which is now nearly 2 decades old), del Zoppo et al9 observed that overall frequency of extracranial ICA recanalization was 8%, and that of MCA stem and distal occlusion were 26.1% and 38.1%, respectively. In the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA (CLOTBUST) trial9 comparing IV rt-PA and continuous TCD (target group) to IV rt-PA alone, 27% vs 13% achieved complete recanalization at 1 hour. Ribo et al10 studied 179 patients with cerebral occlusion treated with IV rt-PA. At 1 hour, the continuous TCD recanalization...
status was partial in 28% and complete in 17%. The probability of recanalization decreased significantly after the first 60 minutes. Another study\(^1\) of 31 patients with documented occlusion on initial CTA found early recanalization (thrombolysis in cerebral infarction (TICI)\(^2\)) at angiogram in 7 (22.6%) patients (mean time between rt-PA and DSA was 120 minutes). Using MRA for recanalization assessment over time after rt-PA therapy, among 42 MCA occlusions (30 M1 and 12 M2), complete recanalization and partial recanalization were observed in 52.3% at 1 hour (19% complete and 33% partial), which increased to 80.9% (47.6% and 3.3%) at 24 hours, with a rate much lower in ICA occlusions.\(^1\)

Observations from previous studies also suggest that recanalization with rt-PA is better with more distal occlusions than proximal and worse for ICA and tandem occlusions, as was observed in our study.\(^1\)–\(^4\)

Because early recanalization is an important determinant of good outcome, assessment for the same is critical after thrombolytic therapy. Timely endovascular recanalization may be a strong consideration when the target vessel oc-

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics and Clinical Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Age, median (25(^{th})–75(^{th}) percentiles)</td>
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<td>TOAST (n)</td>
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<td>Large artery</td>
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<td>Cardioembolic</td>
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<td>Indeterminate</td>
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<td>Other</td>
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<tr>
<td>NIHSS, median (25(^{th})–75(^{th}) percentiles)</td>
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<td>ASPECTS, median (25(^{th})–75(^{th}) percentiles)</td>
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<tr>
<td>Treatment process and outcomes</td>
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<tr>
<td>Onset to rt-PA time, median (25(^{th})–75(^{th}) percentiles), min</td>
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<tr>
<td>Onset to recanalization time, median (25(^{th})–75(^{th}) percentiles), min</td>
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<tr>
<td>Mortality (n)</td>
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<td>mRS score (\leq 2) at 3 months (n)</td>
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IV indicate intravenous; mRS, modified Rankin Scale; rt-PA, recombinant tissue plasminogen activator.

<table>
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<tr>
<th>Table 2. Baseline Occlusions and Proportional Recanalization</th>
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<tr>
<td>Occlusion Location</td>
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<tr>
<td>M1-MCA</td>
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<tr>
<td>ICA terminus (T, L)</td>
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<tr>
<td>M2-MCA</td>
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<tr>
<td>BA</td>
</tr>
<tr>
<td>All</td>
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</table>

BA indicates basilar artery; ICA, internal carotid artery; IV, intravenous; MCA, middle cerebral artery; rt-PA, recombinant tissue plasminogen activator.
included is a proximal T-occlusion or basilar artery occlusion, both of which have a low rate of recanalization after systemic thrombolysis in a given patient. Other issues like spontaneous and delayed recanalization, relationship of early and late recanalization to clinical outcomes, and whether a combined IV intra-arterial approach leads to a better outcome are important. Recanalization has been observed to be associated with good clinical outcome, and recent reanalysis of International Management of Stroke trials and a published RECANALISE study have suggested better outcomes with a shorter time from onset and recanalization. Our findings are consistent with previous data because patients treated with IV rt-PA and those with recanalization were more likely to have a good outcome compared to those with later intra-arterial recanalization. The difference in time to recanalization was almost 90 minutes (215 minutes from onset vs 303 minutes from onset) on average between the 2 groups, which could explain this difference in outcomes. These data provide a novel assessment of thrombolytic effect using baseline CT angiography and early follow-up vascular imaging for comparison. We believe that any study of thrombolysis, whether IV or intra-arterial or both, must include an assessment of the primary treatment target—the vessel. The International Management of Stroke III trial includes a posttreatment assessment of the vessel with 24-hour CTA; however, it remains uncertain what the best time to evaluate vessel status is as a marker of therapeutic efficacy.

There are limitations to this study. It is a retrospectively collected data, and not all patients treated with IV rt-PA underwent angiogram, leading to a potential bias. We did include both the TCD and angiogram data to remove selection bias as much as possible. Within the angiogram group, most patients underwent angiography directly to ascertain recanalization status emergently. Although clinical improvement is an important marker, many patients do not show rapidity of improvement after IV rt-PA. We do feel that waiting for clinical recovery and losing vital time is not justified in general and may produce unnecessary delays to angiography. The true benefit of a combined approach vs standard IV rt-PA can only be ascertained in a randomized trial such as International Management of Stroke III. We have not included patients treated with IV rt-PA in absence of CTA, in whom occlusion localization is likely based on clinical presentation and CT findings. However, we wanted a homogenous cohort of patients, and the same bias could be true of studies using the hyperdense MCA sign as the end point for outcomes.

### Conclusion

In summary, the rate of acute recanalization demonstrated by TCD/angiogram is low in acute ischemic stroke patients treated with IV rt-PA alone and is worse for those with distal ICA and basilar artery occlusions. This is significantly improved with an endovascular approach. Recanalization achieved either with rt-PA or with a combined approach is a strong predictor of a good outcome.

### Acknowledgments

The authors acknowledge the contribution of the entire Calgary stroke program.

### Sources of Funding

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### Disclosures

None.

### References


### Table 3. Multivariable Model and Modified Rankin Scale Score 0 to 2 Outcome

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<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
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<tr>
<td>Recanalization after IV rt-PA</td>
<td>2.7</td>
<td>1.5–4.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recanalization after endovascular treatment</td>
<td>2.0</td>
<td>1.1–3.5</td>
<td>0.009</td>
</tr>
<tr>
<td>No recanalization (reference category)</td>
<td>1</td>
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<td>. . .</td>
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<tr>
<td>bNIHSS</td>
<td>0.96</td>
<td>0.94–0.99</td>
<td>0.001</td>
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<tr>
<td>Hypertension</td>
<td>0.7</td>
<td>0.5–0.9</td>
<td>0.015</td>
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bNIHSS indicates baseline National Institutes of Health Stroke Scale score; CI, confidence interval; IV, intravenous; RR, risk ratio; rt-PA, tissue plasminogen activator.


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Abstract

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Departments of Clinical Neurosciences, Radiology, Medicine, and Community Health Sciences, Foothills Hospital, University of Calgary, Calgary, Alberta, Canada; Department of Neurology, All India Institute of Medical Sciences, New Delhi, India.

Background and Purpose: Recent experience with intravenous recombinant tissue plasminogen activator (rt-PA) in acute ischemic stroke has shown that recanalization rates with this therapy remain low. The purpose of this analysis was to report the rate and outcome of recanalization with rt-PA in a real-world experience of patients with acute ischemic stroke.

Methods: We reviewed consecutive patients with acute ischemic stroke who received rt-PA at a comprehensive stroke center between January 2005 and June 2007. The primary outcome was successful recanalization (Thrombolysis in Cerebral Infarction [TICI] Grades 2 or 3; TCD) in patients who received rt-PA at the presenting hospital. Secondary outcomes included time to recanalization, recanalization rate, and clinical outcomes at 90 days.

Results: In total, 216 patients were treated with rt-PA, and 127 patients underwent TCD monitoring. The overall recanalization rate was 27% (95% CI, 21.25% to 32.78%). The recanalization rates for TICI Grades 2, 2B, and 3 were 26.5%, 23.1%, and 28.4%, respectively. The median time to successful recanalization was 44 minutes (95% CI, 36.5 to 53 minutes).

Conclusion: The overall recanalization rate with intravenous rt-PA was 27% in our experience. These data are consistent with previous studies and support the need for additional randomized trials to determine the efficacy of rt-PA in acute ischemic stroke.

Stroke 2010; 41: 2254-2258

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Multivariable Model Change in Rankin Score (mRS) with rt-PA</th>
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<td>Variable</td>
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<td>p Value</td>
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<td>&lt;0.0001</td>
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<tr>
<td>Baseline NIHSS</td>
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<td>1.1 to 3.5</td>
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<tr>
<td>NIHSS</td>
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bNIHSS is the baseline NIHSS (National Institutes of Health Stroke Scale).