Early reperfusion and clinical outcomes in patients with M₂ occlusion: pooled analysis of the PROACT II, IMS, and IMS II studies

Clinical article

RALPH RAHME, M.D.,¹,² SHARON D. YEATTS, PH.D.,² TODD A. ABRUZZO, M.D.,¹ LINCOLN JIMENEZ, M.D.,¹ LIQIONG FAN, M.D.,³ THOMAS A. TOMSICK, M.D.,¹ ANDREW J. RINGER, M.D.,¹ ANTHONY J. FURLAN, M.D.,⁵ JOSEPH P. BRODERICK, M.D.,⁶ AND POOJA KHATRI, M.D., M.Sc.⁶

Departments of ¹Neurosurgery, ⁴Radiology, and ⁵Neurology, University of Cincinnati, Ohio; ²Department of Neurosurgery, University of Louisville, Kentucky; ³Department of Medicine, Medical University of South Carolina, Charleston, South Carolina; and ⁴Department of Neurology, Case Western Reserve University, Cleveland, Ohio

Object. The role of endovascular therapy in patients with acute ischemic stroke and a solitary M₂ occlusion remains unclear. Through a pooled analysis of 3 interventional stroke trials, the authors sought to analyze the impact of successful early reperfusion of M₂ occlusions on patient outcome.

Methods. Patients with a solitary M₂ occlusion were identified from the Prolyse in Acute Cerebral Thromboembolism (PROACT) II, Interventional Management of Stroke (IMS), and IMS II trial databases and were divided into 2 groups: successful reperfusion (thrombolysis in cerebral infarction [TICI] 2–3) at 2 hours and failed reperfusion (TICI 0–1) at 2 hours. Baseline characteristics and clinical outcomes were compared.

Results. Sixty-three patients, 40 from PROACT II and 23 from IMS and IMS II, were identified. Successful early angiographic reperfusion (TICI 2–3) was observed in 31 patients (49.2%). No statistically significant difference in the rates of intracerebral hemorrhage (60.9% vs 47.6%, p = 0.55) or mortality (19.4% vs 15.6%, p = 0.75) was observed. However, there was a trend toward higher incidence of symptomatic hemorrhage in the TICI 2–3 group (17.4% vs 0%, p = 0.11). There was also a trend toward higher baseline glucose levels in this group (151.5 mg/dl vs 129.6 mg/dl, p = 0.09). Despite these differences, the rate of functional independence (modified Rankin Scale Score 0–2) at 3 months was similar (TICI 2–3, 58.1% vs TICI 0–1, 53.1%; p = 0.80).

Conclusions. A positive correlation between successful early reperfusion and clinical outcome could not be demonstrated for patients with M₂ occlusion. Irrespective of reperfusion status, such patients have better outcomes than those with more proximal occlusions, with more than 50% achieving functional independence at 3 months.

(http://thejns.org/doi/abs/10.3171/2014.7.JNS131430)

Key Words • acute ischemic stroke • intraarterial thrombolysis • middle cerebral artery • outcome • reperfusion • vascular disorders

A solitary occlusion at the M₂ segment of the middle cerebral artery (MCA) is identified as the cause of stroke in 9%–38% of patients in large thrombolysis series, thus accounting for 16%–41% of all MCA infarctions in this population.¹–³,⁵,⁹,¹¹,¹³,¹⁵–¹⁸ Unfortunately, the benefit of aggressive intraarterial (IA) intervention for M₂ occlusions remains unclear and the benefit-risk ratio is debatable. Compared with the M₁ segment of the MCA and the internal carotid artery (ICA), M₂ divisions are more distal vessels with smaller calibers and thinner walls. Thus, endovascular access can be more challenging and risky. Moreover, the involved vascular territory and ischemic penumbra are more limited in size, which inevitably translates into a narrower margin of benefit. In fact, reported recanalization rates in the literature have been highly variable, ranging from 43% to 82%¹,⁸,¹²,¹₆,¹₇ following IA therapy and from 31% to 68% following intravenous (IV) thrombolysis.¹,¹⁵,¹₈ Likewise, rates of favorable clinical outcome have varied between 41% and 76% and

See the corresponding editorial in this issue, pp 1351–1353.
between 48% and 81% after IA therapy and IV thrombolysis, respectively.3,8,12–17

Recently it was suggested that the likelihood of favorable functional outcome following IA intervention for M$_2$ occlusions could be independent of revascularization status.7,13 To help answer this question, namely whether aggressive endovascular revascularization of M$_2$ occlusions is warranted, we performed a pooled analysis of 3 prospective interventional stroke trials: Prolyse in Acute Cerebral Thromboembolism (PROACT) II, Interventional Management of Stroke (IMS), and IMS II. Given that, in all 3 trials, endovascular reperfusion was attempted exclusively via pharmacological means, it is expected that the results of this analysis may not be necessarily applicable to patients undergoing mechanical thrombolysis.

**Methods**

The PROACT II study was an open-label randomized controlled trial conducted in 54 centers in the US and Canada.5 One hundred eighty-eight patients between 18 and 85 years of age, with a National Institutes of Health Stroke Scale (NIHSS) score of ≥4 and an angiographically proven M$_1$ or M$_2$, MCA occlusion, were randomized in a 2:1 ratio to either 9 mg IA recombinant prourokinase (r-proUK) plus low-dose IV heparin (treatment arm) or low-dose IV heparin alone (control arm). Mechanical clot disruption was not allowed, and treatment had to have been started in all patients within 6 hours of symptom onset. Final reperfusion status was defined on control angiograms performed at 2 hours posttreatment, according to the thrombolysis in myocardial infarction (TIMI) grading scale.5 A favorable functional outcome was defined as a modified Rankin Scale (mRS) score of 0–2 at 90 days. Head CTs were obtained at baseline, at 24 hours, and at 7–10 days after treatment. Patients in the treatment arm had higher rates of successful reperfusion (TIMI 2–3) at 120 minutes (66% vs 18%, p < 0.001) and better clinical outcomes at 90 days (mRS Score 0–2: 40% vs 25%, p = 0.04).

The IMS study was an open-label single-arm prospective trial designed to investigate the feasibility and safety of a combined IV-IA approach to recanalization in acute ischemic stroke.8 Eighty patients between 18 and 80 years of age and with NIHSS scores of ≥10 were recruited from 17 North American centers and underwent IV thrombolysis with 0.6 mg/kg (60 mg maximum) recombinant tissue plasminogen activator (r-tPA) within 3 hours of symptom onset. Cerebral angiography with administration of low-dose IV heparin was immediately performed and additional IA r-tPA thrombolysis, with a maximum dose of 22 mg, was administered to patients with persistent large-vessel occlusion. Angioplasty and stenting were not allowed and all patients had to have IA thrombolysis started within 5 hours of symptom onset. Repeat angiograms were performed at 15-minute intervals up to 2 hours of r-tPA infusion or until complete thrombolysis. Final reperfusion status was determined using the modified thrombolysis in cerebral infarction (TICI) scale.7,17

Functional outcome at 3 months was assessed using the mRS. Outcomes were compared with those of age- and NIHSS-matched historical subsets of placebo- and r-tPA-treated patients from the National Institute of Neurological Disorders and Stroke (NINDS) r-tPA Stroke Trial.9,10 The IMS II study9 included 81 additional patients recruited from 13 centers and was methodologically identical to the first IMS study, except that the EKOS microinfusion catheter had to be used whenever possible in appropriate vessels (ICA, M$_1$, M$_2$, vertebral artery, basilary artery). This catheter delivered low-energy ultrasound to potentially aid in IA thrombolysis. Both trials showed very similar results in terms of early angiographic reperfusion (TICI 2–3: 56% in IMS, 60% in IMS II) and clinical outcomes at 3 months (mRS Score 0–2: 43% in IMS, 46% in IMS II). The clinical outcomes were significantly better than those of age- and NIHSS-matched historical controls from the NINDS r-tPA Stroke Trial (mRS Score 0–2: 28%; IMS, OR 2.18 [95% CI 1.20–3.99]; IMS II, OR 2.82 [95% CI 1.54–5.16]). Moreover, clinical outcomes were similar to those of patients receiving IV r-tPA in that trial (mRS Score 0–2: 39%), despite significantly longer median times to initiation of IV r-tPA in the IMS and IMS II studies (IMS, 140 minutes; IMS II, 142 minutes; NINDS r-tPA Stroke Trial, 90 minutes [p < 0.0001]).

For this pooled analysis, 2 authors (T.A.T., P.K.) who were blinded to clinical outcomes reviewed all angiograms from PROACT II, IMS, and IMS II, identified cases in which a solitary M$_2$ occlusion was the target lesion, and classified reperfusion status at 2 hours according to a modified TICI scale (Table 1).7,15 Whenever disagreement occurred, it was resolved by consensus. Patients were divided into 2 groups: successful reperfusion (TICI 2–3) and failed reperfusion (TICI 0–1). The 2 groups were compared in regard to the following: baseline characteristics, functional independence (mRS Score 0–2) at 3 months, intracerebral hemorrhage (ICH), and mortality. For living patients who missed the 3-month follow-up assessment, their most recent mRS score prior to 3 months was used as their final outcome. Given the limited sample size, only univariate analyses were undertaken. All statistical analyses were performed using the SAS/STAT software (SAS Institute, Inc.). The Fisher’s exact test was used for categorical variables and the Mann-Whitney U-test for numerical variables. Statistical significance was set at p < 0.05.

**Results**

A total of 67 solitary M$_2$ occlusions, 44 from PROACT II (30 in the treatment arm, 14 in the control arm) and 23 from the IMS and IMS II studies, were identified. Reperfusion status could not be determined for 4 patients in the PROACT II study (2 in each arm), who were thus excluded from the analysis. The remaining 63 patients, 26 men and 37 women, had a mean age of 65 years and a mean NIHSS score of 16.5. The left side was affected in 42 patients (66.7%). Thirty-one patients (49.2%) were successfully reperfused (TICI 2–3), whereas 32 (50.8%) had persistent occlusion (TICI 0–1) at 2 hours. Patient and stroke characteristics were largely similar between the 2 groups (Table 2). However, patients in the reper-
fused group tended to have higher baseline serum glucose levels (151.5 mg/dl vs 129.6 mg/dl, p = 0.09).

No statistically significant difference in the rates of ICH (TICI 2–3, 60.9%; TICI 0–1, 47.6%; p = 0.55) and mortality (TICI 2–3, 19.4%; TICI 0–1, 15.6%; p = 0.75) was observed between the 2 groups (Fig. 1). However, there was a trend toward higher incidence of symptomatic ICH in reperfused patients (TICI 2–3, 17.4%; TICI 0–1, 0%; p = 0.11). Nonetheless, clinical outcome at 3 months was similar between the 2 groups, with 58.1% (18 of 31 patients) in the reperfused group and 53.1% (17 of 32) in the nonreperfused group achieving mRS scores of 0–2 (p = 0.80).

**Discussion**

In this pooled analysis of 3 interventional stroke trials, we were unable to demonstrate a positive correlation between successful early reperfusion and clinical outcome in patients with acute M2 occlusions. Irrespective of reperfusion status, more than half of the patients achieved functional independence at 3 months. Tomsick et al. previously reported revascularization results in the IMS and IMS II studies. Although only 43.5% of 23 solitary M2 occlusions were successfully recanalized, 69.5% had mRS scores of 0–2 at 90 days. Moreover, 76% of patients with incompletely recanalized lesions achieved a good outcome. The authors concluded that, for M2 occlusions, good outcomes may not be dependent on early revascularization, which may relate to the much smaller volume of ischemic brain compared with more proximal occlusions.

By pooling data from PROACT II as well as IMS and IMS II, we were able to increase statistical power by almost tripling the number of patients with an M2 occlusion. We observed a 5% absolute outcome benefit (mRS 0–2 in 58.1% vs 53.1%) among reperfused patients, which is potentially clinically significant in this patient population. However, this difference did not reach statistical significance. Although the study was underpowered and

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no perfusion</td>
</tr>
<tr>
<td>1</td>
<td>perfusion past the initial obstruction, but limited distal branch filling with little or slow distal perfusion</td>
</tr>
<tr>
<td>2A</td>
<td>perfusion of less than 50% of the vascular distribution of the occluded artery</td>
</tr>
<tr>
<td>2B</td>
<td>perfusion of 50% or more of the vascular distribution of the occluded artery</td>
</tr>
<tr>
<td>3</td>
<td>full perfusion with filling of all distal branches</td>
</tr>
</tbody>
</table>


**TABLE 2: Baseline patient and stroke characteristics in 63 patients in the PROACT II, IMS, and IMS II studies**

<table>
<thead>
<tr>
<th>Variable</th>
<th>TICI 0–1</th>
<th>TICI 2–3</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age (yrs)</td>
<td>64.7 ± 13.9</td>
<td>65.3 ± 13.0</td>
<td>0.86</td>
</tr>
<tr>
<td>male sex</td>
<td>12/32 (37.5%)</td>
<td>14/31 (45.2%)</td>
<td>0.61</td>
</tr>
<tr>
<td>white race</td>
<td>26/32 (81.2%)</td>
<td>23/31 (74.2%)</td>
<td>0.56</td>
</tr>
<tr>
<td>hypertension</td>
<td>19/32 (59.4%)</td>
<td>23/31 (74.2%)</td>
<td>0.29</td>
</tr>
<tr>
<td>mean systolic BP (mm Hg)</td>
<td>149.7 ± 17.7</td>
<td>150.2 ± 20.9</td>
<td>0.95</td>
</tr>
<tr>
<td>mean diastolic BP (mm Hg)</td>
<td>80.5 ± 16.3</td>
<td>82.4 ± 13.6</td>
<td>0.77</td>
</tr>
<tr>
<td>diabetes</td>
<td>6/31 (19.4%)</td>
<td>8/31 (25.8%)</td>
<td>0.76</td>
</tr>
<tr>
<td>mean glucose (mg/dl)</td>
<td>129.6 ± 64.6</td>
<td>151.5 ± 74.8</td>
<td>0.09</td>
</tr>
<tr>
<td>myocardial infarction</td>
<td>6/32 (18.8%)</td>
<td>5/31 (16.1%)</td>
<td>1.00</td>
</tr>
<tr>
<td>congestive heart failure</td>
<td>9/31 (29%)</td>
<td>6/31 (19.4%)</td>
<td>0.55</td>
</tr>
<tr>
<td>cigarette smoking</td>
<td>6/31 (19.4%)</td>
<td>6/31 (19.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>baseline mRS Score 0–1</td>
<td>31/32 (96.9%)</td>
<td>31/31 (100%)</td>
<td>1.00</td>
</tr>
<tr>
<td>mean NIHSS score</td>
<td>16.0 ± 5.6</td>
<td>16.9 ± 5.6</td>
<td>0.62</td>
</tr>
<tr>
<td>mean time to treatment (hrs)</td>
<td>4.1 ± 1.4</td>
<td>3.8 ± 1.6</td>
<td>0.79</td>
</tr>
<tr>
<td>early infarction signs on CT</td>
<td>23/32 (71.9%)</td>
<td>21/31 (67.7%)</td>
<td>0.79</td>
</tr>
<tr>
<td>mean ASPECTS</td>
<td>7.5 ± 1.5</td>
<td>7.5 ± 2.2</td>
<td>0.93</td>
</tr>
<tr>
<td>lt side</td>
<td>22/31 (71%)</td>
<td>20/31 (64.5%)</td>
<td>0.79</td>
</tr>
<tr>
<td>IV thrombolysis</td>
<td>9/32 (28.1%)</td>
<td>14/31 (45.2%)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

* Values are expressed as either the mean ± SD or as n/N (%). ASPECTS = Alberta Stroke Program Early CT Score; BP = blood pressure.
† Calculated using the Fisher’s exact test (categorical variables) or the Mann-Whitney U-test (numerical variables).
Reperfusion of M2 and outcome

Fig. 1. Bar graph showing ICH and mortality rates in patients with an M2 occlusion.

a significant imbalance in baseline serum glucose level favored the nonreperfused group, our data do not support the hypothesis that aggressive early reperfusion of solitary M2 occlusions is beneficial. The limited extent of involved territory, the presence of sufficient leptomeningeal collateral vessels, and the technical challenges and risks related to aggressive endovascular revascularization of an occluded M2 are all potential explanations for this negative result. Notwithstanding, it should be stressed that final reperfusion status in this study was determined at 2 hours and that some patients may have experienced recanalization later. The exact rate of late reperfusion and its impact on final patient outcome are not known.

The role of aggressive IA interventions in patients with acute M2 occlusions is still a matter of controversy.1-6,12-14,16,17 In a large single-center series, Arnold et al.1 achieved TIMI 2–3 reperfusion in 63.2% of 57 M2 occlusions, compared with 77% and 58.1% for M1 and ICA occlusions, respectively. In a pooled analysis of Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi-MERCI trials, Shi et al.16 observed a TIMI 2–3 reperfusion rate of 82.1% among 28 M2 occlusions, contrasting with a rate of favorable clinical outcome at 3 months of only 40.7%. Moreover, M2 occlusions exhibited higher revascularization rates compared with M1 occlusions, with a trend toward better clinical outcomes. Giford et al.6 successfully performed microballoon angioplasty on 7 well-selected patients with M2 and M1 occlusions, achieving remarkably high reperfusion rates with low morbidity and mortality.

In a recent subgroup analysis of PROACT II,12 we showed that, compared with placebo, IA thrombolysis of solitary M2 occlusions was associated with a 3-fold increase in early TICI 2–3 reperfusion, from 16.7% to 53.6% (p = 0.04). Likewise, there was a trend toward a 2-fold increase in the rate of functional independence (mRS 0–2) at 90 days, from 28.6% to 53.3% (p = 0.19). Rai et al.13 analyzed a prospectively maintained database of 223 patients with large-vessel occlusions (ICA, M1, and M2). Irrespective of clot location, endovascular treatment resulted in better clinical outcomes than IV thrombolysis treatment. Among 71 patients with an M2 occlusion, an mRS score of 0–2 was achieved at 90 days by 76% in the endovascular group compared with 47.8% in the IV thrombolysis group. Data from the recently completed IMS III trial,14 which randomized patients with NIHSS scores of ≥ 8 to either IV r-tPA or combined IV r-tPA and IA therapy, may provide additional insight into this matter. This subgroup analysis is currently being conducted by another group of authors, and its results will hopefully come to light in the months to come.

Our study has limitations. Data were pooled from trials with significant differences in design and methodology, particularly in regard to treatment received. Patients in the PROACT II study did not undergo IV thrombolysis and received only low-dose IV heparin, either alone or in combination with IA r-proUK. In contrast, all patients in the IMS and IMS II studies received IV r-tPA followed by low-dose IV heparin and a variable dose of IA r-tPA. As a result, the study population was not perfectly homogeneous. By virtue of the same, there was a substantial difference in median time to treatment between PROACT-II (5 hours) and IMS and IMS II (140 minutes),5,9,15 which could partly explain the better clinical outcomes observed in the IMS trials among patients with M2 occlusions (mRS 0–2: 70% in IMS and IMS II, 45% in PROACT II). Thus, the 55% overall rate of favorable outcomes in this series actually represents an average between PROACT II and IMS cohorts. Interestingly, in PROACT II, IA r-tPA was associated with significantly higher reperfusion rates, translating into a trend toward improved functional outcomes in the treatment group.12 This association was completely lost in the IMS trials,15 possibly as a result of the routine use of IV r-tPA leading to higher rates of ICH among reperfused patients.

It would have been interesting to analyze outcome by time to reperfusion in the reperfused group. However, time to reperfusion was not available for PROACT II patients. Moreover, this study was relatively underpowered due to the limited sample size, and there was some baseline imbalance in serum glucose level between reperfused and nonreperfused patients. These factors may have contributed to the negative results. Likewise, in all 3 trials, endovascular reperfusion was achieved via pharmacological thrombolysis rather than mechanical means. Thus, these results may not be generalizable to patients with M2 occlusions who undergo mechanical thrombolysis. Specifically, the rate of symptomatic ICH in the reperfused group could possibly have been reduced by the use of mechanical rather than pharmacological techniques, which could have led to significantly improved functional outcomes in this population.

Finally, it would have been interesting to analyze the impact of leptomeningeal collateral vessels on outcome, given that the presence of these vessels is expected to be a major prognosticator for patients in whom reperfusion fails. Unfortunately, these data were available only in PROACT II. In the IMS and IMS II studies, the status of leptomeningeal collaterals was not routinely assessed and many patients underwent only single-vessel cerebral angiograms. However, despite all these limitations, this is the largest study to date examining the impact of early reperfusion on outcome in patients with acute ischemic stroke secondary to M2 occlusion. Furthermore, in all 3
trials, angiographic and clinical assessments were rigorously conducted and outcome end points were largely similar, which allowed data pooling and made a meaningful statistical analysis possible.

Conclusions

Irrespective of reperfusion status at 2 hours, patients with M2 occlusions seem to have better outcomes than patients with more proximal occlusions, with functional independence being achieved by > 50% of patients at 3 months. Whether successful reperfusion could further improve patient outcome, particularly if rapidly accomplished, remains to be seen.

Acknowledgments

We thank the Statistical Center at the Medical University of South Carolina (statistical support), the Greater Cincinnati/Northern Kentucky Stroke Team (critical paper review), and the PROACT II, IMS, and IMS II Investigators (source of data) for their valuable contributions to this work.

Disclosure

Supported by NIH/NINDS K23 grant no. NS059843 (Dr. Kha-tri). Dr. Yeatts is a consultant for Genentech. Dr. Furlan was Principal Investigator in the PROACT II study. Dr. Broderick received clinical or research support for the study described from Genentech; Concentric, Inc.; and EKOS Corp.

Author contributions to the study and manuscript preparation include the following. Conception and design: Rahme, Abruzzo, Tomrick, Renger. Analysis and interpretation of data: all authors. Drafting the article: Rahme. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Rahme. Statistical analysis: Yeatts. Administrative/technical/material support: Yeatts, Jimenez, Fan, Furlan.

References