Revascularization End Points in Stroke Interventional Trials

Recanalization Versus Reperfusion in IMS-I

Pooja Khatri, MD; Joddi Neff, MD; Joseph P. Broderick, MD; Jane C. Khoury, MS; Janice Carrozella, RN; Thomas Tomsick, MD; for the IMS-I Investigators

Background and Purpose—The acute stroke literature lacks a standard convention regarding the critical end point of revascularization. Two distinct parameters may be clinically important: (1) recanalization of the primary arterial occlusive lesion (AOL) and (2) global reperfusion of the distal vascular bed. We sought to determine their relationship in the Interventional Management of Stroke (IMS) Phase I trial of combined intravenous (IV) and intraarterial (IA) recombinant tissue plasminogen activator.

Methods—Sixty-one angiograms were reanalyzed using recanalization and reperfusion scores. The AOL Score was defined as: 0=no recanalization of the primary occlusion, I=incomplete or partial recanalization of the primary occlusion with no distal flow, II=incomplete or partial recanalization of the primary occlusion with distal flow, or III=complete recanalization of the primary occlusion with distal flow. The Thrombolysis in Myocardial Infarction (TIMI) Score was defined as: 0=no perfusion, 1=perfusion past the initial occlusion but no distal branch filling, 2=perfusion and incomplete or slow distal branch filling, or 3=full perfusion with filling of all distal branches. We compared the 2 scores with one another and with good clinical outcome (modified Rankin Score zero to 2).

Results—AOL and TIMI scores showed modest agreement (kappa, 0.30; confidence interval, 0.16 to 0.44). Good clinical outcome was seen in 49% of patients with AOL II/III scores (P=0.055) and 54% with TIMI 2/3 scores (P=0.019). The 2 methods did not significantly differ in predicting outcome (P=0.13).

Conclusions—AOL recanalization and TIMI reperfusion scores comparably predict clinical outcome in this treatment paradigm. Other modalities may show different relationships between these 2 revascularization end points. Future studies should distinguish between these parameters semantically and methodologically. (Stroke. 2005;36:2400-2403.)

Key Words: acute Rx ■ acute stroke ■ interventional neuroradiology

Thrombolytic revascularization is the only proven, effective way to reverse neurologic deficit in acute ischemic stroke.1 Newer revascularization strategies are often assessed, at least in part, based on their ability to restore flow. In addition, the U.S. Food and Drug Administration (FDA) assesses devices for revascularization according to their ability to restore blood flow.2 However, despite attempts to define reporting standards for thrombolysis trials,3 the acute stroke literature currently lacks a standard convention for describing this critical end point. Trials, studies, and case series have used the terms “recanalization” and “reperfusion,” or sometimes both interchangeably, to describe revascularization. Moreover, definitions of each term vary.

Two distinct parameters that may be critical in the assessment of revascularization are (1) recanalization of the primary arterial occlusive lesion (AOL) and (2) global reperfusion of the distal vascular bed. Distinguishing between these parameters may be clinically important. For example, an artery may be completely recanalized, but distal clot embolization may limit distal reperfusion. This may limit significant neurologic recovery and could theoretically increase the risk of hemorrhage as a result of local hyperperfusion in ischemic brain regions. On the other hand, distal reperfusion may be achieved, but the artery may have incomplete recanalization (ie, residual clot at the primary occlusive site) predisposing to a higher rate of reocclusion with subsequent clinical deterioration.4 Drugs, devices, or combinations may differ in their ability to achieve and maintain recanalization and reperfusion.

Heterogeneous end points have been used in recent trials and studies. PROACT-I and PROACT-II, the only randomized trials of intraarterial thrombolytic therapy, defined their revascularization end points as reperfusion using the Thrombolysis in Myocardial Infarction (TIMI) scoring method5 per the protocol but reported restoration of the M1 and M2 segments as TIMI 3 flow.6,7 IMS-I used the term “recanalization” to refer to reperfusion using TIMI criteria requiring normal perfusion into M3 and M4 segments for TIMI 3 designation.8 Others, including the EKOS Microlysis ultrasound infusion catheter feasibility study and the MERCI-I
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pilot study of the nitinol corkscrew retrieval device, have used recanalization as an end point but have quantified it using the TIMI score.9–11

Modified or novel scoring systems have been proposed as well. For example, recanalization has been graded as complete, incomplete or partial, or none.12–14 More discriminate versions of the TIMI reperfusion score have been proposed, dividing the TIMI score into 53,15 or 6 grades such as the Thrombolysis in Cerebral Infarction (TICI) grading system.3,16 Other strategies have included combining recanalization and reperfusion into one score,17–19 assessing the grade of thrombus at the site of occlusion with TIMI nomenclature,15 and accounting for clot location within modified revascularization scoring systems.20 These scales have not been compared or validated in large-scale trials.

With these concerns regarding the terminology and scoring of revascularization in mind, we reexamined the angiographic data from the Interventional Management of Stroke (IMS) phase I trial of combined low-dose intravenous recombinant tissue plasminogen activator (rtPA) (0.6 mg/kg) within 3 hours of stroke onset followed by intraarterial (IA) rtPA (up to 22 mg) within 7 hr. We sought to determine the relationship between recanalization and reperfusion. To minimize confusion, the TIMI scoring method was reserved for reperfusion assessment, not recanalization at the primary occlusive site. A second scoring system, the primary arterial occlusive lesion (AOL) recanalization scoring method, was defined to focus on recanalization. We hypothesized that TIMI reperfusion and AOL recanalization scores are not equivalent, and measuring recanalization would not predict clinical outcome as well as measuring TIMI reperfusion in the IMS-I study.

Methods

The IMS-I Pilot Study was a 17-center, open-label, single-arm pilot study designed to investigate the feasibility and safety of a combined intravenous (IV) and IA approach to recanalization using rtPA. Eighty subjects with ischemic stroke and a baseline NIHSSS 10 or more were treated within 3 hours, followed by up to 22 mg IA rtPA for a maximum of 2 hours of infusion or until thrombolysis was achieved. Detailed methods and results of the IMS-I study are published elsewhere.8 All 61 angiograms of subjects who received both IV and IA rtPA were reanalyzed.

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TABLE 1. AOL and TIMI Score Definitions

<table>
<thead>
<tr>
<th>Score</th>
<th>AOL Recanalization</th>
<th>TIMI Reperfusion</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>No recanalization of the primary occlusive lesion</td>
<td>0</td>
</tr>
<tr>
<td>I</td>
<td>Incomplete or partial recanalization of the primary occlusive lesion with no</td>
<td>Perfusion past the initial branch filling</td>
</tr>
<tr>
<td>II</td>
<td>Incomplete or partial recanalization of the primary occlusive lesion with any</td>
<td>Perfusion with incomplete or slow distal branch filling</td>
</tr>
<tr>
<td>III</td>
<td>Complete recanalization of the primary occlusion with any distal flow</td>
<td>Full perfusion with filling of all distal branches, including M3, 4</td>
</tr>
</tbody>
</table>

TABLE 2. Cases Grouped by AOL and TIMI Scores

<table>
<thead>
<tr>
<th>TIMI 0</th>
<th>TIMI 1</th>
<th>TIMI 2</th>
<th>TIMI 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOL 0</td>
<td>11</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>AOL I</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>AOL II</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>AOL III</td>
<td>0</td>
<td>5</td>
<td>21</td>
</tr>
</tbody>
</table>

AOL recanalization and TIMI reperfusion are shown in Table 1. Both scores were determined for each subject who received both IV and IA rtPA. Scores were generated by the 3 readers (P.K., J.N., T.T.) based on consensus.

Blinded modified Rankin Scores (mRS) at 3 months poststroke onset were collected as part of the IMS-I trial.

The 2 score systems were compared for agreement using the kappa statistic. χ2 analysis was used to compare reperfusion and recanalization (TIMI 2/3 and AOL II/III, respectively) to good clinical outcome. Good clinical outcome was defined as mRS zero to 2 (ie, mild or no disability, with independent performance of activities of daily living) as predefined by the IMS-I trial. The 2 scoring methods were compared with each other as related to predicting good clinical outcome, using receiver operator characteristic (ROC) analysis.

Results

The median AOL score was III (interquartile range [IQR] 1 to 3). The median TIMI score was 2 (IQR 1 to 2). The 2 scoring methods showed only modest agreement (kappa, 0.30; confidence interval [CI], 0.16 to 0.44). Table 2 shows cases grouped by AOL and TIMI scores, suggesting a greater discrepancy between these methods at higher scores. For example, only 19% (6 of 32) of patients with complete recanalization (AOL=III) had complete reperfusion (TIMI=3).

AOL and TIMI scores are listed by score grade and good clinical outcome in Table 3. There was a significant relationship between TIMI 2/3 and good outcome (P=0.019). The relationship between AOL II/III and good outcome did not reach statistical significance (P=0.055). Specifically, 21 of 43 (48.8%) subjects with AOL II/III had good outcomes, whereas 18 of 33 (54.5%) TIMI 2/3 subjects had good outcomes. Conversely, 14 of 43 (77.8%) patients with AOL 0–I and 21 of 28 (75.0%) subjects with TIMI zero to one had poor outcomes. Using ROC analysis, the area under the curve for the AOL scores was 0.586 (standard error [SE] 0.076) and for TIMI scores was 0.651 (SE 0.073), suggesting no statistically significant difference between these 2 scoring methods in predicting clinical outcome (P=0.13).

The relationships between combined AOL and TIMI grades and clinical outcomes are shown in Table 4. When combined scores were ranked, designating AOL and TIMI
zero to one as lowest and AOL and TIMI 2/3 as highest, higher score combinations were associated with higher rates of good outcome by the Cochran-Armitage test for trend ($P=0.02$).

### Discussion

In the IMS-I paradigm of a combined IV/IA thrombolysis approach, TIMI and AOL scores had only modest agreement. Although some agreement is to be expected, because better opening of the arterial occlusive lesion should lead to more flow to the distal vascular bed, clearly these terms are not synonymous. Moreover, although this result cannot be generalized to other treatment paradigms, it suggests that these terms should be distinguished semantically and methodologically in the literature. Treatment-specific factors such as distal embolization rates and frequency of the reocclusion of partially recanalized arteries may lead to better or worse agreement in these 2 measures of revascularization.

The discrepancy between scoring methods was highest among those with higher scores, highlighting the importance of distinguishing these revascularization features in acute stroke studies and reports. Most studies have used grades 2/3 to define their recanalization end points whether they used recanalization TIMI or reperfusion TIMI scores.6,10,21,22

We also found that TIMI scores of 2/3 were associated with good clinical outcome ($P=0.019$). Although AOL scoring did not reach statistical significance ($P=0.055$), the 2 scoring methods did not differ significantly in their prediction of clinical outcome using ROC analysis ($P=0.13$). In another series of patients treated with IA thrombolytic therapy, with or without prior IV therapy, a similar association between TIMI (zero/one vs 2/3) and outcome (rehabilitation/home vs nursing home/death) was seen ($P=0.018$).16 Of note, we cannot assert that either revascularization parameter is a valid surrogate end point based on this univariate analysis.

These data suggest that prior descriptions of revascularization by either parameter may be valid. However, both the absolute and relative clinical significance of recanalization and reperfusion scores may be different in treatment paradigms other than the IMS-I combined IV/IA approach.

It has become common practice to compare phase I and II revascularization trials with historic controls. In addition, the U.S. Food and Drug Administration approval of devices requires only surrogate end points comparable to previous methods.2 For these comparisons to be valid, we must use the same end points with the same prespecified definitions.

We propose that analyses of revascularization reserve “recanalization” for the restoration of flow at the primary occlusive lesion (or each subsequent branch beyond, where defined) and “reperfusion” for restoration of flow to the terminal vascular branches arising from that primary arterial site. To minimize ambiguity, we also suggest that TIMI or related terminologies such as TICI be used strictly to describe reperfusion as evaluated by arteriographic analysis. Instead of using a “local” TIMI to describe recanalization of a specific occlusion, it may be less confusing to use either the AOL recanalization terminology described here or some other validated measure as it becomes available. These conventions are being applied in the IMS-II trial, in which the EKOS Microlysis ultrasound catheter has been incorporated into the combined IV/IA approach. Other revascularization methods, including drugs, devices, or combinations of both, should be examined for both recanalization and reperfusion end points. With these distinctions, we hope to gain a deeper understanding of not only how intracranial revascularization therapies differ, but also how they impact clinical outcome.

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