Infarct Volume Is a Pivotal Biomarker After Intra-Arterial Stroke Therapy

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Background and Purpose—Pretreatment infarct volume appears to predict clinical outcome after intra-arterial therapy. To confirm the importance of infarct size in patients undergoing intra-arterial therapy, we sought to characterize the relationship between final infarct volume (FIV) and long-term functional outcome in a prospective cohort of endovascularly treated patients.

Methods—From our prospective intra-arterial therapy database, we identified 107 patients with acute ischemic stroke with anterior circulation proximal artery occlusions who underwent final infarct imaging and had 3-month modified Rankin Scale scores. Clinical, imaging, treatment, and outcome data were analyzed.

Results—Mean age was 66.6 years. Median admission National Institutes of Health Stroke Scale score was 17. Reperfusion (Thrombolysis In Cerebral Infarction 2A–3) was achieved in 78 (72.9%) patients. Twenty-seven (25.2%) patients achieved a 3-month good outcome (modified Rankin Scale 0–2), and 30 (28.0%) died. Median FIV was 71.4 cm³. FIV independently correlated with functional outcome across the entire modified Rankin Scale. In receiver operating characteristic analysis, it was the best discriminator of both good outcome (area under the curve = 0.857) and mortality (area under the curve = 0.772). A FIV of approximately 50 cm³ demonstrated the greatest accuracy for distinguishing good versus poor outcome, and a FIV of approximately 90 cm³ was highly specific for a poor outcome. The interaction term between FIV and age was the only independent predictor of good outcome (P<0.0001). The impact of FIV was accentuated in patients <80 years.

Conclusions—Among patients with anterior circulation acute ischemic stroke who undergo intra-arterial therapy, final infarct volume is a critical determinant of 3-month functional outcome and appears suitable as a surrogate biomarker in proof-of-concept intra-arterial therapy trials. (Stroke. 2012;43:1323-1330.)

Key Words: acute stroke ■ imaging ■ infarct volume ■ intra-arterial therapy

Proximal cerebral artery occlusions (PAOs) represent 30% to 40% of acute ischemic strokes but account for the majority of poor outcomes.1 Intra-arterial therapy (IAT) has emerged as an effective means of revascularization2 and is increasingly used to treat this devastating disease. Currently, IAT is guided primarily by the time from symptom onset or last seen well.3–5 However, data are lacking regarding whether this approach improves clinical outcomes. Based on recent prospective open-label studies, it is clear that outcomes are highly variable.3,5 Some of the poor outcomes are certainly related to delayed or incomplete reperfusion, which may reflect the presence of recalcitrant clots (eg, fibrous clot or excessive clot burden).6,7 However, poor patient selection is likely responsible for many of the dismal outcomes.8 For this reason, Stroke Therapy Academic Industry Roundtable (STAIR) committee recommendations have advocated the use of advanced neuroimaging for patient selection in randomized controlled trials to test the efficacy of IAT.9

Unfortunately, it remains unclear which neuroimaging findings identify patients with PAO who are good treatment candidates. Among patients with anterior circulation PAO, recent studies suggest that pretreatment infarct size influences outcome after IAT.10,11 Specifically, small baseline infarct size predicts improved outcome. To confirm the importance of infarct volume in this population, we sought to characterize the relationship between final (posttreatment) infarct volume (FIV) and long-term functional outcome in a prospective database of endovascularly treated patients.

Methods

We identified all patients with anterior circulation acute ischemic stroke treated between January 2005 and December 2009 (n=144) in
our prospective observational IAT database. Study criteria included (1) evaluable follow-up neuroimaging (CT or MRI) between 24 hours and 2 weeks after stroke; and (2) available 3-month modified Rankin Scale (mRS) score. Thirty-seven (25.7%) patients were excluded. Seventeen patients lacked follow-up imaging beyond 24 hours; 1 lacked clinical follow-up; and 2 lacked both. Seven patients were excluded for baseline functional dependence (pseudomobility mRS ≥ 3). Additional patients were excluded due to bitemporal stroke (n = 1), hemiconraniectomy (n = 2), parenchymal hematoma Type 2 (n = 3), and poor image quality (n = 4), findings that were felt to confound infarct size determination or the relationship between infarct size and clinical outcome. Clinical, imaging, treatment, and outcome data were retrospectively analyzed. This study was conducted with Institutional Review Board approval and was compliant with the Health Insurance Portability and Accountability Act.

Treatment and Outcome Evaluation
At our institution, IAT is performed in patients who are ineligible for or refractory to intravenous tissue-type plasminogen activator (IV tPA). IV tPA is administered within the 0- to 4.5-hour window per guidelines recommendations. As long as there is no clinical improvement during infusion, patients who are potentially eligible for IAT will undergo further imaging and evaluation, including CT angiography, to identify a proximal cerebral artery occlusion. No repeat vessel imaging is performed after completion of IV tPA and before IAT. Indications for IAT include (1) proximal occlusion (internal carotid artery, middle cerebral artery M1/M2 branches); (2) noncontrast CT without hemorrhage or large (more than one third middle cerebral artery territory) parenchymal hypodensity; (3) significant neurological deficit (National Institutes of Health Stroke Scale score [NIHSSS] ≥ 8); and (4) treatment < 8 hours from onset/last seen well. Informed consent is obtained before IAT from the patient or healthcare proxy.

IAT is performed under general anesthesia using thrombolytic and/or mechanical devices. Although there is no standardized protocol for performing IAT at our institution, we typically use mechanical devices first, because we believe that they can achieve reperfusion more quickly. We always use Food and Drug Administration-approved devices (Mercretriever or Penumbra system) first unless they cannot be delivered to the occlusion site (eg, due to vessel tortuosity). If the patient is treated within 6 hours from onset, then a thrombolytic agent (urokinase or recombinant tissue-type plasminogen activator) may be used as an adjunct with or without microwave maceration. For clots that are refractory to these methods, we may attempt off-label angioplasty and/or stent placement. These rescue methods are discussed with the stroke neurologist, and decisions are individualized depending on the patient’s circumstances.

Reperfusion was assessed using the Thrombolysis in Cerebral Infarction (TICI) scale. Good clinical outcome was defined as 3-month mRS score = 0 to 2 (functional independence).

Imaging Protocols
Noncontrast CT was performed on helical scanners (LightSpeed 16 or 64; GE Medical, Milwaukee, WI) using helical mode (1.25-mm thickness, 120 kV, 250 mA) and reconstructed as 5-mm thick axial sections.

MRI was performed on a 1.5-Tesla Signa whole-body scanner (GE Medical). Diffusion imaging was performed using a single-shot echoplanar spin-echo sequence with 2 180° radiofrequency pulses to minimize eddy current warping. Five images/slice were acquired at b = 0 s/mm² followed by 5 at b = 1000 s/mm² in 6 directions (TR/TE 5000/80–110 ms, field of view 22 cm, matrix 128×128 zero-filled to 256×256, 5-mm slice thickness, 1-mm gap). Fluid-attenuated inversion recovery imaging was performed using TR/TE 9000/120 to 140 ms, field of view 22 cm, matrix size 224×256, 5-mm thickness, 1-mm gap.

Imaging Analysis
Final infarcts were outlined on noncontrast CT or MRI diffusion/fluid-attenuated inversion recovery scans by an experienced neuro-radiologist (A.J.Y.) using Analyze 10.0 (AnalyzeDirect, Overland Park, KS). Infarcts were outlined on MRI whenever available. For noncontrast CT, window/level settings were adjusted to maximize contrast between the normal and infarcted brain. In cases with significant cerebral edema, volume increases from swelling were accounted for by excluding infarcted tissue that extended across midline or produced ventricular effacement (compared with pretreatment ventricular configuration). Edema producing sulcal effacement was not excluded. Given the early subacute imaging, there were no cases with tissue loss. Imaging evaluation was blinded to all information except stroke side. FIV in cubic centimeters was calculated.

Statistical Analysis
Variables were tested for Spearman correlation with mRS score. Variables with significant correlation were tested in multiple regression. Univariate analysis of dichotomized outcomes used the Student t test (normally distributed data reported as mean ± SD), Mann–Whitney test (ordinal data reported as median and interquartile range), and χ² test (categorical data reported as proportions). Variables with univariate P < 0.20 were tested in multiple logistic regression. Receiver operating characteristic curves were used to characterize the test performance of univariate predictors. Areas under the receiver operating characteristic curves (AUC) were compared using the nonparametric approach of DeLong et al. Continuous variables were tested for normality (Kolmogorov-Smirnov test). Statistical analyses were performed using MedCalc 11.2.1 (Mariakerke, Belgium). Probability value < 0.05 was considered significant.

Results
Baseline Variables, Treatment Data, and Outcomes
Among the 107 study patients, mean age was 66.6 years; 50.5% were female; and 56.1% were left-sided strokes (Table 1). Median admission NIHSSS was 17. Vessel occlusion sites included tandem cervical/intracranial (n = 8), internal carotid artery terminus ± middle cerebral artery (n = 29), middle cerebral artery M1 segment (n = 61), and M2 segment (n = 9). Forty-five (42.1%) patients received full-dose IV tPA. Mean time from stroke onset/last seen well to groin puncture was 323.2 minutes. Endovascular treatments included thrombolysis (26.2%) and/or mechanical devices (78.5%). TICI 2A–3 reperfusion was achieved in 78 (72.9%) patients. At 3 months, 27 (25.2%) patients achieved a good outcome (mRS 0–2), and 30 (28.0%) died. Median FIV was 71.4 cm³. Median time from ictus to final infarct imaging was 41.8 hours, and the modality was CT in 58.9%.

Correlation Between FIV and mRS Score
There was a significant correlation between FIV and 3-month mRS (r = 0.592; P < 0.0001). TICI score, age, NIHSSS, and hypertension also correlated with mRS (Table 2) but demonstrated weaker correlation than FIV. In multiple regression, only FIV, age, and TICI score were independent predictors of 3-month mRS.

Predictors of 3-Month Good Outcome (mRS 0–2)
In univariate analysis, smaller FIV, higher TICI score (greater reperfusion), lower admission NIHSSS, and younger age were associated with functional independence (Table 3). Only FIV (OR, 0.968; 95% CI, 0.951–0.985; P = 0.0002) and age (OR, 0.934; 95% CI, 0.897–0.972; P = 0.0007) were indepen-
Table 1. Baseline Variables, Reperfusion, and Clinical/Imaging Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.6 ± 17.0</td>
</tr>
<tr>
<td>Female (%)</td>
<td>54 (50.5%)</td>
</tr>
<tr>
<td>Admission NIHSS score</td>
<td>17 (IQR, 14–20)</td>
</tr>
<tr>
<td>Admission DWI lesion volume, cm³ (n=75)</td>
<td>15.5 (IQR, 9.8–28.8)</td>
</tr>
<tr>
<td>Left hemisphere (%)</td>
<td>60 (56.1%)</td>
</tr>
<tr>
<td>Level of occlusion (%)</td>
<td></td>
</tr>
<tr>
<td>Tandem cervical ICA/intracranial occlusion</td>
<td>8 (7.5%)</td>
</tr>
<tr>
<td>Intracranial ICA</td>
<td>29 (27.1%)</td>
</tr>
<tr>
<td>MCA M1 segment</td>
<td>61 (57.0%)</td>
</tr>
<tr>
<td>MCA M2 segment</td>
<td>9 (8.4%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>73 (68.2%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>24 (22.4%)</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>49 (45.8%)</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>40 (37.4%)</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>36 (33.6%)</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>16 (15.2%)</td>
</tr>
<tr>
<td>History of stroke/TIA, %</td>
<td>10 (9.4%)</td>
</tr>
<tr>
<td>IV tPA administration (%)</td>
<td>45 (42.1%)</td>
</tr>
<tr>
<td>IA thrombolytic administration (%)</td>
<td>28 (26.2%)</td>
</tr>
<tr>
<td>IA mechanical, % Merci and/or Penumbra</td>
<td>84 (78.5%)</td>
</tr>
<tr>
<td>Time from last seen well to groin puncture, min</td>
<td>323.2 ± 140.9</td>
</tr>
<tr>
<td>Reperfusion (TICI score 0–3)</td>
<td>2A (IQR, 1–2B)</td>
</tr>
<tr>
<td>Time to final imaging, h</td>
<td>41.8 (IQR, 28.3–75.0)</td>
</tr>
<tr>
<td>CT scan (versus MRI) as final imaging modality (%)</td>
<td>63 (58.9%)</td>
</tr>
<tr>
<td>Final infarct volume, cm³</td>
<td>71.4 (IQR, 33.2–175.1)</td>
</tr>
<tr>
<td>3-mo clinical outcome (mRS)</td>
<td>4 (IQR, 2–6)</td>
</tr>
</tbody>
</table>

Data are reported as mean ± SD, median (IQR), or percentage. NIHSS indicates National Institutes of Health Stroke Scale; DWI, diffusion-weighted imaging; ICA, internal carotid artery; MCA, middle cerebral artery; TIA, transient ischemic attack; IV tPA, intravenous tissue-type plasminogen activator; IA, intra-arterial; TICI, Thrombolysis In Cerebral Infarction; IQR, interquartile range; mRS, modified Rankin Scale.

Table 2. Variables With Significant Correlation to 3-Month mRS (0–6)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rho</th>
<th>95% CI</th>
<th>Univariate P</th>
<th>Multivariate P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final infarct volume, cm³</td>
<td>0.592</td>
<td>0.453 to 0.703</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.399</td>
<td>0.226 to 0.547</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TICI score (0–3)</td>
<td>−0.512</td>
<td>−0.640 to −0.357</td>
<td>&lt;0.0001</td>
<td>0.0006</td>
</tr>
<tr>
<td>Admission NIHSSS</td>
<td>0.284</td>
<td>0.100 to 0.450</td>
<td>0.004</td>
<td>NS</td>
</tr>
<tr>
<td>HTN</td>
<td>0.200</td>
<td>0.011 to 0.376</td>
<td>0.04</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note: mRS indicates modified Rankin Scale; TICI, Thrombolysis In Cerebral Infarction; NIHSSS, National Institutes of Health Stroke Scale score; HTN, hypertension; NS, nonsignificant.

Predictors of Mortality

Univariate predictors of mortality were larger FIV (P < 0.0001), lower TICI score (P = 0.0004), older age (P = 0.01), and higher significance (P = 0.753), although this did not reach statistical significance (P = 0.10).

FIV in the range of 40 to 50 cm³ demonstrated the greatest accuracy for identifying a good outcome (sensitivity, 74.1%–81.5%; specificity, 77.5%–85.0%). Figure 2 illustrates the marked improvement in mRS scores with FIV < 50 cm³. FIV > 80 to 90 cm³ demonstrated high (approximately 85%–90%) specificity for poor outcome (Table 4). Only 2 of 45 (4.4%) patients with infarct sizes > 100 cm³ had good outcomes (108.9 and 116.1 cm³).

Predictors of Mortality

Univariate predictors of mortality were larger FIV (P < 0.0001), lower TICI score (P = 0.0004), older age (P = 0.01), and higher

In acute ischemic stroke secondary to anterior circulation proximal artery occlusion, smaller final infarct volume is the single best predictor of both 3-month functional independence and survival when evaluated against known important variables including age, baseline NIHSSS, occlusion level, and reperfusion. Moreover, there is a significant interaction between FIV and age such that the clinical impact of FIV is more pronounced in patients < 80 years old. Among these
patients, a moderate to strong correlation exists between FIV and functional outcome across the entire mRS.

Previous evidence in milder strokes demonstrates that final infarct size is a key determinant of outcome. In a substudy of the Acute Stroke Accurate Prediction (ASAP) trial involving 169 patients with median NIHSS score (mild to moderate severity), infarct growth was an independent predictor of 90-day mRS 0 to 1. In a subgroup analysis of Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET), which included 72 patients with median NIHSS score (moderate to severe strokes), FIV had a strong correlation with 90-day NIHSS score (r=0.81; P<0.01). Our study extends these findings to major strokes (median NIHSS score =17) secondary to PAO.

Conflicting data exist regarding the use of infarct size as a surrogate end point in stroke trials. However, validation

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Bar graphs depict the proportion of good outcomes (mRS 0–2) by final infarct volume strata for (A) the entire population and (B) patients <80 years. mRS indicates modified Rankin Scale.
of any surrogate biomarker relies heavily on the patient population and clinical end point of interest.\textsuperscript{19} Our findings support FIV as a suitable surrogate end point in proof-of-concept trials involving patients with major stroke with PAO. For the end point of 3-month mRS 0 to 2, which is commonly used in IAT trials, our study reveals an AUC=0.86 for FIV, which is above the accepted benchmark for biomarker validation (AUC ≥0.8).\textsuperscript{20} Based on this finding, infarct growth may be a better end point for new intra-arterial device trials than Thrombolysis in Myocardial Ischemia/TICI 2 to 3 revascularization (AUC=0.66 in our data set). As expected, there was a statistically significant negative correlation ($\rho=-0.46, P<0.0001$) between TICI reperfusion and FIV in our data set (ie, greater reperfusion was associated with smaller final infarct volume). For studies using a shift analysis across the Rankin Scale, FIV may be a suitable biomarker only in patients with PAO <80 years old. The rank correlation coefficient between FIV and mRS in this patient group is 0.67, which approaches the accepted standard of 0.7.\textsuperscript{19}

It is noteworthy that admission NIHSSS was not an independent predictor of outcome in our analysis. There are several potential explanations. First, our patients constituted a broadly homogeneous population with severe neurological deficit (92.5% [99 of 107] with NIHSSS 11–30). This level of deficit in the Prolyse in Acute Cerebral Thromboembolism (PROACT) II control group was associated with an 80.4% rate of 3-month poor outcome (mRS 3–6).\textsuperscript{21} The natural history of our cohort was likely worse, because approximately 30% had terminal internal carotid artery occlusions and approximately 20% were >85 years old (PROACT II exclusions). Therefore, a floor effect may have existed whereby NIHSSS variations within our cohort did not produce significant changes in their overall poor natural history. Second, pretreatment NIHSSS not only reflects the extent of the infarct core, but also of the clinical penumbra and would not be expected to correlate with patient outcome when significant penumbral tissue has been rescued. Final infarct size, on the other hand, incorporates treatment effect. Lastly, it has been demonstrated that FIV correlates strongly with long-term neurological deficit among nonlacunar hemispheric strokes.\textsuperscript{16,22} This may explain the strong relationship between FIV and clinical outcome seen in our study and the lack of an incremental contribution by the NIHSSS at baseline. Tissue eloquence appears to play a more critical role in small-vessel strokes in which small lesions may be located almost entirely in ineloquent brain matter compared with very large hemispheric strokes in which there is little chance of this.\textsuperscript{22}

Our finding that age influences the clinical effect of infarct size is reasonable when one considers that very elderly patients are more likely to have comorbidities and stroke-related complications (eg, pneumonia, pulmonary embolus), which can result in poor functional outcome despite a small infarct size. In a retrospective analysis of the pooled Mechanical Embolus Removal in Cerebral Ischemia (MERCi) and Multi MERCI trials,\textsuperscript{23} hypertension, diabetes, and atrial fibrillation each demonstrated a statistically significant association with poor 90-day outcome (mRS 3–6). When combined into a 4-point chronic disease score (1 point for the presence of each condition), they independently predicted functional outcome in addition to age, NIHSSS, and reperfusion. The rates of good outcome were 51% for 0 points, 34% for 1 point, 27% for 2 points, and 12% for 3 points. Moreover, elderly patients have higher rates of in-hospital medical complications, which have been shown to independently predict death and disability.\textsuperscript{24} Other factors that may hamper stroke recovery in this population include reduced neuronal plasticity, poorer social supports, and baseline disability.\textsuperscript{25} Finally, the aggressiveness of care may not be as high in elderly patients, because many have previously expressed wishes limiting life-sustaining care should their prognosis for recovery of independent living be poor. A recent study has demonstrated that patients >80 years old have higher mortality and reduced independence after intravenous alteplase, which the authors attributed to increased stroke complications.\textsuperscript{26}

The importance of infarct size among patients with PAO supports the growing evidence that pretreatment infarct volume predicts the clinical response to IAT.\textsuperscript{10,11} Because early revascularization significantly limits infarct growth,\textsuperscript{10,16} it follows that initial infarct size will approximate final infarct size and hence correlate with clinical outcome in successfully treated patients. Patients who do not undergo reperfusion are highly likely to do poorly regardless of baseline infarct size. Only 1 (3.4%) of 29 patients without vessel recanalization

| Table 4. Final Infarct Volume Thresholds With High Specificity for Poor Outcome (mRS >2) |
|-------------------------------|---------------------------------|-------------------|-----------------|-----------------|
| Volume Threshold, cm$^3$       | Specificity (95% CI) for Poor Outcome | OR (95% CI) for Poor Outcome | P Value |
| >80                            | 85.2% (66.3%–95.8%)               | 8.63 (2.73–27.3)   | <0.0001         |
| >90                            | 88.9% (70.8%–97.5%)               | 10.3 (2.86–37.0)   | <0.0001         |
| >100                           | 92.6% (75.7%–98.9%)               | 14.5 (3.22–65.5)   | <0.0001         |
| >110                           | 96.3% (81.0%–99.4%)               | 27.3 (3.54–211.2)  | <0.0001         |
| >120                           | 100% (87.1%–100%)                 | ...               | ...             |

mRS indicates modified Rankin Scale.
had a good outcome in this study. Her initial NIHSSS was 13, and her final infarct volume was 109 cm$^3$. She had a 90-day mRS score of 2. Her good outcome was likely related to her young age (19 years old) and the fact that her stroke involved the right (nondominant) hemisphere.

Specific volume thresholds in our study may help to guide clinical trials and practice. An infarct size threshold of approximately 50 cm$^3$ demonstrates the highest accuracy for distinguishing good versus poor functional outcome among endovascularly treated patients. For future IAT trials, selecting patients with pretreatment infarct size <50 cm$^3$ may yield the greatest power for demonstrating a clinical response to early reperfusion. Additionally, we have demonstrated that an infarct size >90 cm$^3$ has a high (approximately 90%) specificity for 3-month mRS score ≥2. This threshold may be clinically useful for identifying patients for whom the risks of treatment, particularly symptomatic intracerebral hemorrhage, outweigh the benefits. In a study of 645 patients with anterior circulation stroke treated with intravenous or intraarterial thrombolysis, Singer et al$^{27}$ demonstrated a 16.1% rate of symptomatic intracerebral hemorrhage among patients with pretreatment diffusion lesion volume >100 cm$^3$, which is higher than the 4.4% rate of good outcome observed in infarcts of this size in our study.

We excluded patients with parenchymal hematoma Type 2 bleeds from our analysis for 2 main reasons. First, the mass effect associated with these hematomas would artificially inflate infarct volume. Second, because parenchymal parenchymal hematoma Type 2 has been shown to be an independent predictor of early neurological deterioration and death at 3 months,$^{28}$ inclusion of these bleeds would alter the relationship between infarct size and clinical outcome, particularly if they occurred within small- to moderate-sized infarcts. This last point is particularly important for estimating the risk–benefit ratio of IAT. In this calculation, one must balance the major risk of symptomatic intracerebral hemorrhage against the benefit among patients who do not incur this complication. As mentioned in the preceding paragraph, our analysis suggests that patients with large baseline infarcts (eg, >90–100 cm$^3$) will have a minimal chance at a good recovery, which is overshadowed by the elevated risk of symptomatic intracerebral hemorrhage.

The Acute Stroke Imaging Research Roadmap highlighted several unresolved questions including what are the optimal timing and modality for final infarct imaging and are these related to treatment type.$^{29}$ We have demonstrated that in patients undergoing IAT, early subacute imaging within the first week is highly predictive of clinical outcome. This is consistent with data from EPITHET demonstrating that infarct size at 3 days after IV tPA is highly correlated with 90-day NIHSSS and performs as well as 90-day lesion volume.$^{16}$ Moreover, FIV determined at very early time points (24–41.8 [study median] hours poststroke) correlates with clinical outcome as well as (and possibly better than) FIV determined later in the subacute period. This supports previous studies, which have found small increases (2.9–4.4 cm$^3$) in mean/median infarct size between 24 to 48 hours and 1 week poststroke.$^{30,31}$ Taken together, these findings suggest that the majority of infarcts go on to completion between the first and second day and that the benefits of IAT are achieved by this point. Further lesion growth beyond this time is probably related to edema, which is maximal at 3 to 5 days.

The predictive power of infarct size at such early times facilitates its use as a surrogate biomarker in patients with proximal occlusions. For IAT trials, the main advantage of this approach would be to prevent the loss to follow-up seen with later imaging times. In clinical practice, FIV determined within the first few days may be useful for early prognostication after IAT. In the early posttreatment period, it is often difficult to obtain a reliable neurological examination due to intubation or medical complications. In addition, imaging may be useful to predict delayed neurological recovery from ischemic stunning.$^{32}$

With respect to imaging modality, there were no significant differences in outcome prediction using MRI versus CT. However, MRI demonstrated a numerically higher correlation coefficient and a larger area under the receiver operating characteristic curve suggesting that it may be better than CT given a larger sample size. This is plausible considering the better infarct visualization on MRI in the early poststroke period.

Study limitations include exclusion of approximately 25% of the available patients in our database, which was mostly related to lack of adequate imaging. However, after removing the patients with baseline mRS >2 (n=7), there were no significant differences in the major clinical variables (age, NIHSSS, and occlusion level), degree of reperfusion, and clinical outcomes between patients who were included versus excluded in the analysis. The only significant difference was an increase in congestive heart failure among excluded patients (42.3% versus 15.2%; P=0.005). Second, we did not assess reliability of lesion measurement. However, intra- and interrater reliability for manual outlining of final infarct size has been demonstrated to be high for MRI and CT, particularly for infarcts >10 cm$^3$.$^{16,33–35}$ Mean differences are on the order of 1 to 3 cm$^3$, which is much less than between-subject variability. This measurement error also compares favorably to the reported variance for clinical scales such as National Institutes of Health Stroke Scale and mRS.$^{33}$ Third, we recognize that our conclusions regarding the use of infarct volume thresholds for treatment selection require validation using pretreatment infarct volumes. Unfortunately, we could not test our proposed thresholds in this data set due to the absence of a sufficient number of large baseline infarcts (>70–100 cm$^3$), which have been shown to predict poor outcome despite reperfusion.$^{10,36}$ Of 75 patients with available pretreatment diffusion-weighted imaging in our study cohort, only 11 patients had infarcts >50 cm$^3$ (6 were >90 cm$^3$). The median admission diffusion-weighted imaging infarct volume was 15.5 cm$^3$. This skew toward smaller pretreatment infarct volumes derives from the fact that our patients were selected for IAT largely based on the presence of a small infarct. Small baseline infarcts by themselves do not predict outcomes, because they may remain stable or progress depending on the degree and timing of reperfusion.$^{10}$ This is reflected in our broad range of final infarct sizes. Fourth, despite the fact that final infarct volume was a very strong predictor of functional outcome after endovascular
therapy, it is likely that adding lesion location information to volume measurement would further enhance outcome prediction among patients undergoing IAT, particularly for small to moderate-sized final infarcts.37 However, additional research including clinical and imaging validation is necessary before lesion topography can be used to accurately and reliably predict outcome in the clinical setting. For instance, brain functions require intact networks of anatomically distinct regions; therefore, the clinical impact of lesion topography should account for functional connectivity within these networks.38 Fifth, we used an 8-hour window for IAT. However, the optimal time window remains uncertain.39 Based on PROACT II and other studies,21,40,41 it appears that the therapeutic window is longer for IAT than for IV tPA. This may be related to physiological differences between PAOs (IAT-eligible) and more distal occlusions. There are more potential pathways for collateralization in the setting of proximal occlusions, and the strength of the collateral circulation has been demonstrated to influence revascularization results and infarct growth after endovascular therapy.42 In patients with good collaterals, substantial volumes of viable penumbral tissue may persist between 12 and 24 hours from stroke onset.43 Importantly, in our study, final infarct volume was a significant predictor of outcome both for patients treated within the 4.5-hour window and for those treated beyond this time. Finally, our volume analysis did not fully account for edema-related lesion growth. Although we were able to remove brain swelling that produced midline shift and ventricular effacement, we did not account for sulcal effacement. However, inclusion of edema volume may enhance clinical prediction by identifying those patients with a malignant edema pattern. Further work is required to validate reliable measures of edema.

Conclusions

We have demonstrated that in acute ischemic stroke secondary to anterior circulation PAO, final infarct volume is a critical determinant of 3-month functional outcome and appears suitable as a surrogate end point in proof-of-concept IAT studies. The impact of infarct size is accentuated in patients <80 years. Our findings provide further support for the use of pretreatment infarct size for identifying patients who may benefit from IAT.

Disclosures

Dr S Yoo and Gonzalez receive research support from Penumbra, Inc. Dr Lev receives research support from GE Healthcare and is consultant to Co-Axia, GE Healthcare, and Millennium Pharmaceuticals.

References


Infarct Volume Is a Pivotal Biomarker After Intra-Arterial Stroke Therapy

Stroke. 2012;43:1323-1330; originally published online March 15, 2012;
doi: 10.1161/STROKEAHA.111.639401
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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/43/5/1323

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