The Interventional Management of Stroke III randomized controlled trial failed to demonstrate the benefit of bridging therapy over intravenous tissue-type plasminogen activator (tPA) alone within 3 hours of acute ischemic stroke onset.1 A major limitation of this trial was that pretreatment vessel imaging was not mandated for entry. Among the 47% of patients with documented vessel occlusion, there was a significant benefit of intra-arterial therapy (IAT) in the trial.2 Nevertheless, vessel imaging may also have significant limitations for identifying patients who will benefit from a bridging approach. In an Interventional Management of Stroke III secondary analysis, there was no difference in good outcome rates between the treatment arms for patients with documented middle cerebral artery (MCA) M1 segment occlusions (48% versus 51% for bridging versus intravenous tPA, respectively). These lesions account for a large fraction of anterior circulation proximal artery occlusions. Therefore, there is a clinical need to define imaging biomarkers of intravenous tPA resistance for rapid, appropriate patient selection for early window IAT.

Background and Purpose—Thin-section noncontrast computed tomography images can be used to measure hyperdense clot length in acute ischemic stroke. Clots ≥8 mm have a very low probability of intravenous tissue-type plasminogen activator recanalization and hence may benefit from a bridging intra-arterial approach. To understand the prevalence of such clots, we sought to determine the distribution and predictors of clot lengths in consecutive anterior circulation proximal artery occlusions.

Methods—Of 623 consecutive patients with acute ischemic stroke, 53 met inclusion criteria: presentation <8 hours from onset; intracranial internal carotid artery-terminus or proximal-middle cerebral artery occlusion; admission thin-slice noncontrast computed tomography (≤2.5 mm); and no intravenous tissue-type plasminogen activator pretreatment. For each patient, hyperdense clot length was measured and recorded along with additional relevant imaging and clinical data.

Results—Mean age was 70 years, and mean time to computed tomography was 213 minutes. Median baseline National Institutes of Health Stroke Scale was 16.5. Occlusions were located in the internal carotid artery-terminus (34% [18 of 53]), middle cerebral artery M1 (49% [26 of 53]) and M2 segments (17% [9 of 53]). Hyperdense thrombus was visible in 96%, with mean and median clot lengths (mm) of 18.5 (±14.2) and 16.1 (7.6–25.2), respectively. Occlusion location was the strongest predictor of clot length (multivariate, P=0.02). Clot length was ≥8 mm in 94%, 73%, and 22% of internal carotid artery-terminus, M1, and M2 occlusions, respectively.

Conclusions—The majority of anterior circulation proximal occlusions are ≥8 mm long, helping to explain the low published rates of intravenous tissue-type plasminogen activator recanalization. Internal carotid artery-terminus occlusion is an excellent marker for clot length ≥8 mm; vessel-imaging status alone may be sufficient. Thin-section noncontrast computed tomography seems useful for patients with middle cerebral artery occlusion because of the wide variability of clot lengths. (Stroke. 2013;44:3553-3556.)

Key Words: clot-length ▪ hyperdense MCA ▪ intra-arterial therapy ▪ IV-tPA ▪ stroke

The Interventional Management of Stroke III randomized controlled trial failed to demonstrate the benefit of bridging therapy over intravenous tissue-type plasminogen activator (tPA) alone within 3 hours of acute ischemic stroke onset.1 A major limitation of this trial was that pretreatment vessel imaging was not mandated for entry. Among the 47% of patients with documented vessel occlusion, there was a significant benefit of intra-arterial therapy (IAT) in the trial.2

Nevertheless, vessel imaging may also have significant limitations for identifying patients who will benefit from a bridging approach. In an Interventional Management of Stroke III secondary analysis, there was no difference in good outcome rates between the treatment arms for patients with documented middle cerebral artery (MCA) M1 segment occlusions (48% versus 51% for bridging versus intravenous tPA, respectively). These lesions account for a large fraction of anterior circulation proximal artery strokes. Therefore, there is a clinical need to define imaging biomarkers of intravenous tPA resistance for rapid, appropriate patient selection for early window IAT.

Thin-section noncontrast computed tomography (NCCT) can be used to measure clot lengths accurately on the basis of vessel hyperdensity.3 Hyperdense clot lengths ≥8 mm have a very low probability of intravenous tPA recanalization and may represent an ideal target for bridging IAT.4 To understand the proportion of patients demonstrating this finding, we sought to determine the distribution and predictors of clot lengths in consecutive anterior circulation proximal artery occlusions.
Methods

The study was approved by our institutional review board, which waived written informed consent for this Health Insurance Portability and Accountability Act-compliant retrospective analysis. Between August 2011 and August 2012, we reviewed consecutive patients with acute ischemic stroke who presented to the emergency department. Study inclusion criteria were presentation <8 hours from stroke onset, admission stroke-protocol head NCCT with available thin-slice images (≤2.5 mm), computed tomography angiography (CTA)–documented occlusion of the internal carotid artery-terminus (ICA-T) or proximal MCA (M1, M2), and no intravenous tPA treatment before imaging.

Imaging

CT was performed using a 64-slice multidetector CT (LightSpeed, GE-Healthcare, WI) in helical mode: 120 kV, Auto-mA with noise-index: 3.5, pitch 0.531:1, rotation speed 0.5 seconds, reconstructed with 90% ASiR, soft kernel, field-of-view 22 cm. Axial 0.625-mm images were reformatted to 5-mm-thick maximum intensity projection images. CTA was performed at 120 kV, Auto-mA (noise-index, 12), rotation speed 0.5 seconds. A total of 80- to 100-mL nonionic contrast agent (Omnipaque 370; Nycomed, Roskilde, Denmark) was injected, followed by 40 mL saline, at a rate of 4 mL/s. Images were reconstructed at 0.625 mm thickness at 0.625-mm interval.

Statistics

Clot length was analyzed as a continuous variable, as well as dichotomized, on the basis of 8-mm cutoff as a marker of intravenous tPA resistance. Inter-rater agreement and univariate and multivariate analyses were performed using MedCalc software (version 11.6.1.0; Ostend, Belgium); statistical significance was set at 2-tailed P value <0.05.

Image Analysis

Two neuroradiologists (A.J.Y. with >10 years and L.T.M. with >2 years of clinical experience) measured the hyperdense clot length, if present, on axial and coronal maximum intensity projection-NCCT images with window width and level of 50 HU. To avoid foreshortening, the longer measurement was used for subsequent analysis and reporting.

Table. Patient Characteristics and Predictors of Clot Length

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients (n=53)</th>
<th>Clot Length (&lt;8 mm; n=15)</th>
<th>Clot Length (≥8 mm; n=38)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Univariate</td>
</tr>
<tr>
<td>Age, y; mean (±SD)</td>
<td>70.1 (±16.6)</td>
<td>66.6 (±13.4)</td>
<td>72.4 (±17.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>Sex (women), % (n)</td>
<td>57% (30/53)</td>
<td>47% (7/15)</td>
<td>60% (23/38)</td>
<td>0.38</td>
</tr>
<tr>
<td>Admission NIHSS, median (IQR)</td>
<td>16.5 (11–20)</td>
<td>11 (5.25–17.75)</td>
<td>18 (14.5–20)</td>
<td>0.02</td>
</tr>
<tr>
<td>ASPECTS, median (IQR)</td>
<td>8 (6–9)</td>
<td>8 (6.5–10)</td>
<td>7.5 (5–9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Occlusion side (right), % (n)</td>
<td>53% (28/53)</td>
<td>73% (11/15)</td>
<td>45% (17/38)</td>
<td>0.07</td>
</tr>
<tr>
<td>Occlusion level, % (n)</td>
<td>ICA-T 34% (18/53)</td>
<td>6% (1/18)</td>
<td>94% (17/18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>M1-MCA 49% (26/53)</td>
<td>27% (7/26)</td>
<td>73% (19/26)</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>M2-MCA 17% (9/53)</td>
<td>78% (7/9)</td>
<td>22% (2/9)</td>
<td>0.39</td>
</tr>
<tr>
<td>Onset-to-CT time, mean (±SD)</td>
<td>3.33 (±3.55)</td>
<td>2.31 (±1:37)</td>
<td>3.59 (±4:29)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

ASPECTS indicates Alberta Stroke Program Early CT score; CI, computed tomography; ICA-T, internal carotid artery-terminus; IQR, interquartile range; MCA, middle cerebral artery; and NIHSS, National Institutes of Health Stroke Scale score.

*Continuous, ordinal, and discrete variables are compared with unpaired t test, Mann–Whitney U test, and Fisher exact test, respectively.
Results
Of 623 consecutive patients with acute ischemic stroke, 53 who met the study inclusion criteria were analyzed. Eighty patients had anterior circulation occlusion on the basis of admission CTA <8 hours of stroke onset; however, 27 patients were excluded on the basis of transfer from an outside hospital where intravenous tPA was given before CT imaging at our center. Baseline characteristics are provided in the Table.

Hyperdense thrombus was visible in 96% of patients (2 M1-MCA clots were not visible on thin-section NCCT). Mean (±SD) clot length (mm) was 18.5 (±14.2), and 72% (38 of 53) of clots were ≥8 mm. By occlusion level, mean clot lengths (mm) were 24.6, 17.6, and 8.7 for ICA-T, M1, and M2 occlusions, respectively (P<0.001). Bland–Altman plot revealed no significant difference between 2 observer measurements (Figure 1). In stepwise linear regression, the only independent predictor of clot length was occlusion level (P=0.008).

For dichotomized clot length (<8 versus ≥8 mm), interobserver agreement was almost perfect (κ=0.91; 95% confidence interval, 0.79–1.00). Univariate predictors of ≥8-mm clot were more proximal occlusion level and higher baseline National Institutes of Health Stroke Scale score (Table). By occlusion level, 94% of ICA-T, 73% of M1-MCA, and 22% of M2-MCA clots were ≥8 mm long. In binary logistic regression, clot location was the only independent predictor of clot length was occlusion level (P=0.008).

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Discussion
This study confirms that ≥90% of anterior circulation proximal occlusions are visible as hyperdense clot using thin-section NCCT. The majority (72%) of these occlusions have extensive (≥8 mm) clot burden, further suggesting a sizeable population who may potentially benefit from an intravenous IAT bridging approach (Figure 2).

The observed recanalization efficiency of intravenous tPA based on clot location may correlate with the likelihood of a clot length ≥8 mm at that location. For example, the proportions of short (<8 mm) clots that we found in ICA-T (6%) and M1 (27%) occlusions closely approximate previously reported rates of early intravenous tPA recanalization (4.4% for ICA-T and 32.3% for M1).

Furthermore, these findings have important implications for rapid patient triage to intervention. Currently, many centers wait ≥30 minutes to assess for intravenous tPA failure before sending a patient to IAT.7 However, this same delay has been associated with a 10% relative reduction in the probability of good outcome.8 Because virtually all ICA-T occlusions are ≥8 mm long, it is reasonable to use CTA-evidence of ICA-T occlusion to triage patients directly to IAT during intravenous tPA infusion. This approach is supported by Interventional Management of Stroke III, which demonstrated a 4× higher rate of good outcome after bridging therapy in patients with CTA-documented ICA-T occlusions.2

However, clot length measurement may be critical for triaging proximal MCA occlusions. In Interventional Management of Stroke III, there was an equivalent rate of good outcome (≈50%) between the treatment arms for M1 occlusions.5 By removing the 25% to 30% of M1 clots that are short and likely to respond to intravenous tPA alone, patients who may benefit from catheter-based therapy may be rapidly triaged to the interventional suite. This approach is being tested in the THERAPY randomized trial.

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Clot Length Distribution and Predictors in Anterior Circulation Stroke: Implications for Intra-Arterial Therapy

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