Multimodal CT-Assisted Thrombolysis in Patients With Acute Stroke
A Cohort Study

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Background and Purpose—The value of multimodal CT to assist thrombolysis has received little attention in stroke.

Methods—We assessed prospectively the impact derived from the routine application of CT perfusion and CTA in patients with acute stroke treated consecutively with alteplase. The safety and efficacy of thrombolytic therapy were compared in 106 patients assisted with CT/CTA/CT perfusion (multimodal CT group) and 262 patients assisted without full multimodal brain imaging (control group) during a 5-year period (2005–2009).

Results—Good outcome (modified Rankin scale score ≤2) at 3 months was increased in the multimodal group compared with controls (adjusted OR, 2.88; 95% CI, 1.50–5.52). Multimodal-assisted thrombolysis yielded superior benefits in patients treated beyond 3 hours (adjusted OR, 4.48; 95% CI, 1.68–11.98) than treated within 3 hours (adjusted OR, 1.31; 95% CI, 0.80–2.16; interaction test P=0.043). Mortality (14% and 15%) and symptomatic hemorrhage (5% and 7%) were similar in both groups.

Conclusions—Multimodal CT use in routine clinical practice may heighten the overall efficacy of thrombolytic therapy in acute ischemic stroke. The benefits seem greater in patients treated >3 hours after stroke onset, but further randomized clinical trials are needed to confirm these findings. (Stroke. 2011;42:1129-1131.)

Key Words: imaging ■ neuroradiology ■ thrombolysis

Multimodal MR has been used to assess brain tissue viability and to identify acute stroke candidates for reperfusion therapy in time windows beyond currently accepted limits.1-3 However, few centers have 24-hour per day 7-day per week access to MR, and brain CT perfusion and CTA could offer practical advantages given their greater availability and simpler postprocessing requirements.4

In retrospective studies,4,5 multimodal CT was comparable to MR in assisting acute stroke management, but larger prospective studies are required to define the value of multimodal CT. Here, we analyzed the safety and efficacy of thrombolytic therapy in patients assisted with CT/CTA/CT perfusion (multimodal CT group) and in a control group of consecutive patients who during a 5-year study period received thrombolysis without assistance of full multimodal brain imaging.

Patients and Methods
The study was approved by an Internal Review Board and patients or proxies signed a written informed consent if thrombolysis was to be administered off-label (see online Supplement available at http://stroke.ahajournals.org). All patients were treated in an acute stroke unit at our center (~800 stroke admissions per year). Symptomatic hemorrhage was defined as any hemorrhage and worsening of at least 4 points on the NIHSS attributable to the hemorrhage. Good outcome was defined as a modified Rankin scale score ≤2 at day 90 by investigators blinded to imaging data. CTA and CT perfusion maps were obtained as described in Supplemental Methods. Clinical and imaging data were collected prospectively and all imaging studies were assessed by investigators blinded to prognostic data. Multimodal CT was routinely performed because our tertiary center was catalogued as a comprehensive stroke center in October 2008. Binary and ordinal multivariate logistic regression models were used, including sensitivity analyses with propensity score methods.

Results
There were 106 patients in the multimodal CT group and 262 patients in the control group, including 224 with only plain CT and 38 with CT and CTA performed. There were no significant differences between the study groups at baseline except for the proportions of patients treated >3 hours after stroke and those treated with endovascular therapy (Table). In
binary logistic regression, good functional outcome was increased in the multimodal CT group in models adjusted for age, gender, NIHSS, glucose, and treatment delay or modality (adjusted OR, 2.88; 95% CI, 1.50–5.52). The odds of shifting to a better class in the ordered categories of the modified Rankin scale was also increased in the multimodal CT group (adjusted OR, 2.00; 95% CI, 1.18–3.46; Figure 1). In a sensitivity analysis (Figure 2), multimodal-assisted therapy provided greater benefits in patients treated >3 hours after stroke onset (adjusted OR, 4.48; 95% CI, 1.68–11.98; interaction test \( P = 0.043 \)). Mortality (14% and 15%), and incidence of symptomatic intracerebral hemorrhage (5% and 7%) were similar in patients receiving multimodal-assisted treatment and in controls.

**Discussion**

The main finding of this large cohort study was that patients treated in routine clinical practice with multimodal CT-assisted thrombolysis did significantly better at 3 months than did patients who received the therapy without this assistance. The absolute increased proportion of patients with good outcome (modified Rankin scale score ≤2) was 15%. The study also found that multimodal CT-assisted thrombolysis was particularly beneficial in patients receiving thrombolysis beyond 3 hours of stroke onset, thus expanding previous observations gathered in MRI-based studies. Overall, these results suggest that CT perfusion and CTA may accurately identify the patients with arterial occlusions and ischemic tissue at risk, allowing the recognition of candidates to receive primary or rescue reperfusion therapies beyond currently accepted time limits. Further support of the value of multimodal CT is that a greater proportion of patients in this group was treated beyond 3 hours. Reassuringly, the increased proportion of patients with good outcome was not offset by an increased mortality or bleeding complications, suggesting that CT perfusion and CTA also contributed to withhold the administration of rescue therapies in patients at high risk for complications.

Potential limitations to the study were the lack of an untreated group and that the availability of multimodal CT was not randomized. Contrarily, there were no changes in the

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**Table. Main Characteristics of the Study Population**

<table>
<thead>
<tr>
<th></th>
<th>Controls (N=262)</th>
<th>Multimodal CT (N=106)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>73.0 (65.0–81.0)</td>
<td>73.3 (65.2–81.6)</td>
<td>0.356</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>150 (57)</td>
<td>55 (52)</td>
<td>0.348</td>
</tr>
<tr>
<td>Baseline NIHSS, median (IQR)</td>
<td>10 (5–18)</td>
<td>9 (4–17)</td>
<td>0.510</td>
</tr>
<tr>
<td>Glucose, g/L, mean (SD)</td>
<td>143 (55)</td>
<td>137 (47)</td>
<td>0.375</td>
</tr>
<tr>
<td>Minutes to treatment, median (IQR)</td>
<td>135 (108–170)</td>
<td>140 (107–205)</td>
<td>0.197</td>
</tr>
<tr>
<td>Time to treatment &gt;3 hr, n (%)</td>
<td>42 (16)</td>
<td>30 (28)</td>
<td>0.003</td>
</tr>
<tr>
<td>Complete/partial occlusion at baseline, n (%)</td>
<td>23/38 (60.5)</td>
<td>64/106 (60.4)</td>
<td>0.963</td>
</tr>
<tr>
<td>Endovascular therapy, n (%)</td>
<td>29 (11)</td>
<td>27 (26)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.

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**Figure 1.** Modified Rankin scale at 90 days in multimodal-assisted patients and controls. mRS indicates modified Rankin scale.

**Figure 2.** Main outcome measures according to treatment delay in the study groups. mRS indicates modified Rankin scale; sICH, symptomatic intracranial hemorrhage.
general or specific treatment of stroke during the 5 years of the study, and advanced imaging was routinely performed once our center was cataloged as a comprehensive stroke center, thus limiting the risk of bias. Moreover, patients undergoing multimodal CT and the control group disclosed similar traits at stroke baseline.

Conclusions
In summary, the study suggests that systematic availability of multimodal CT scan in routine clinical practice may increase the global effectiveness of thrombolytic therapy in patients with acute stroke and extend the time window of thrombolyis beyond currently accepted limits. However, further randomized trials will be needed to confirm these results and to establish the value of multimodal CT to assist thrombolytic therapy in acute stroke.

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Disclosure
None.

References
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Supplemental Methods

Thrombolytic treatment allocation

From January 2005 to September 2008, intravenous administration of alteplase was selected in patients admitted within 3 h of stroke onset, while endovascular treatment (ET) was used in few patients admitted >3h of stroke onset according to the judgment of the treating physicians and availability. In October 2008, we were qualified as a CSC implying that CT, CTP, CTA and neurointerventionalism were systematically available at stroke admission. Since then, patients were treated with thrombolytic therapy within 4.5 h of stroke onset. CTP/CTA was performed after alteplase therapy had been infused for 40 minutes and if CTP/CTA disclosed proximal occlusions and ruled out a Malignant profile ET was initiated. In patients admitted > 4.5 h of stroke onset (n=13), or in wake-up strokes (n=6), CTP and CTA were performed before treatment onset and the patients were considered eligible to receive ET when a target mismatch and a proximal occlusion were present and there was not a malignant profile.

Brain imaging

CT scanning was obtained on a 64-row scanner. For CTP, serial CT was performed with a rapid bolus injection of contrast material and four adjacent 7.2mm thick sections were obtained per second for 40 seconds. Anatomic coverage was adjusted to the level of the basal ganglia when anterior circulation infarct was suspected, parallel and superior to the orbital roof. In posterior
circulation infarct, the anatomical imaging reference used to position the dynamic perfusion studies was the internal auditory canal. CTA with maximum intensity projection (MIP) was used to assess location of the occlusion and cerebral blood volume (CBV), cerebral blood flow (CBF) and time to peak (TTP) maps were calculated using a commercially available semi-automated perfusion analysis software (Siemens) based on the maximum slope model of perfusion. Maximum slope of the time attenuation curves (TAC) were used to calculate CBF, and CBV values were calculated from the maximum enhancement ratio. Infarct core was segmented based on a CBV threshold of 0.6 relative to the contralateral white matter,¹ and ischemic penumbra was segmented based on a TTP threshold of 6 seconds for identification of critically hypoperfused tissue.² Infarct core was visually demonstrated on CBV color maps and ischemic penumbra on TTP color maps based on the color scale. Infarct core and tissue at risk volumes were calculated by two independent readers (LO and SC) not involved in the acute care of the patients, with the summation area technique, manually drawing the area of core infarct on each of the parametric CBV images, and the hypoperfused tissue on the TTP images, respectively. The volume of penumbra was calculated as the total volume of TTP abnormality minus the reduced CBV volume and the percentage of mismatch was calculated according to the formula \((TTP - CBV)/TTP\). We defined several imaging patterns similar to those reported in previous MRI studies, but we redefined the criteria according to the smaller brain volume covered by CTP as follows: Target mismatch: Abnormal TTP ≥ 4ml and abnormal \((TTP-CBV)/TTP\) ≥ 50%; No target mismatch: Abnormal \((TTP-CBV)/TTP\) < 50% (small lesion profile excluded); Small lesion: reduced CBV and abnormal TTP volumes both < 4ml; Malignant profile: reduced CBV ≥ 40ml.
Supplemental references


