Is it Time to Reassess the SITS-MOST Criteria for Thrombolysis?
A Comparison of Patients With and Without SITS-MOST Exclusion Criteria

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Background and Purpose—The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) established guidelines to increase safety in acute stroke thrombolysis, but precluding treatment in an important proportion of patients. We aimed to assess safety/efficacy of thrombolysis in patients with SITS-MOST exclusion criteria.

Methods—369 nonlacunar tPA-treated patients were studied. Patients were classified as SITS-MOST (SM) or non–SITS-MOST (NSM) according to SITS-MOST–criteria fulfilling. Clinical evaluation was assessed by NIHSS and functional outcome by mRS at 3 months (functional independency=mRS=2).

Results—Baseline NIHSS was 17. 169 (45.8%) patients were SM and 200 (54.1%) NSM. Recanalization (47.6%/50.3%, P=0.36), 24-hour-improvement (55.6%/49.5%, P=0.114), and SICH were similar (4.8%/5.1%, P=0.554). At discharge, clinical improvement in SM-group was higher (66.7%/55.7%, P=0.024). NSM tended to higher mortality (10.5%/16.1%, P=0.084) and lower functional independence (48.7%/39.6%, P=0.082).

Conclusion—Thrombolysis may be safe in patients not fulfilling SITS-MOST criteria. Testing thrombolysis in patients outside SITS-MOST could be considered in the future. (Stroke. 2009;40:2568-2571.)

Key Words: acute stroke ■ Doppler ■ thrombolysis ■ tPA ■ guidelines

The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) was an observational study aimed to evaluate safety of tPA in clinical practice. It showed similar or even better results than a pool of previous randomized trials, however using very strict patient selection criteria. We hypothesize that these criteria could preclude treatment in an important proportion of patients, and designed a study to evaluate safety and efficacy of thrombolysis outside SITS-MOST.

Patients and Methods
Two retrospective groups were established from our prospective thrombolysis-database.: the SITS-MOST (SM) group and the Non–SITS-MOST (NSM) group.

SITS-MOST Group
Patients fulfilling published SITS-MOST criteria† (during the recruitment period, patients were also included in the SITS-MOST registry) were classified as SM.

Non–SITS-MOST Group
Not fulfilling-patients were subsequentially evaluated according to our institutional preestablished protocol, approved by the local ethic committee, and treated with tPA after informed-consent signature. Requirements included : (1) documented intracranial occlusion; (2) <6 hours stroke with mismatch on multiparametric MRF; (3) International Normalized Ratio (INR) <1.8; (4) Age, clinical stroke severity, or Diabetes Mellitus and previous symptomatic stroke (DM+stroke) were not contraindications; (5) other tPA-contraindications (>6-hour time window, recent stroke, extent lesion on neuroimaging, severe comorbidity/disability) constituted exclusion from treatment and from the study.

To make more comparable both groups, only clinical nonlacunar strokes with a documented intracranial arterial occlusion were included.

Outcomes
Outcomes included: Primary, symptomatic intracranial hemorrhage (SICH); Secondary, recanalization, short-term evolution, and functional outcome.

Clinical/Vascular Evaluation
Stroke severity was sequentially assessed by the National Institute of Health Stroke Scale(NIHSS), defining: deterioration, increase of ≥4points or in-hospital death; improvement, decrease of ≥4points or complete recovery.

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Recanalization after 2 hours (47.6%/52.4%, \( P=0.360 \)) and clinical improvement after 24 hours (SM 55.6%/NSM 49.5%, \( P=0.144 \)) were similar in SM and NSM patients. Likewise, the rate of intracranial hemorrhage (SM 27%/NSM 28.2%; \( P=0.772 \)) and SICH (SM 4.8%/NSM 5.1% \( P=0.554 \) according to SITS-MOST, and 10.2% in both according to NINDS) were comparable. At discharge, SM patients had more frequently clinical improvement (66.7%/55.7%, \( P=0.024 \)). Mortality tended to be higher in NSM (16.1%/10.5%, \( P=0.084 \)), and there was a trend toward better functional outcome in SM (48.3%/39.6%, \( P=0.082 \); Figure).

The different outcomes of subgroups in NSM are shown in the Figure. When we excluded patients >80 years in the NSM-group, the functional outcome was similar to those fulfilling SITS-MOST (mRS \( \leq 2 \) in NSM <80 years: 45.8%, \( P=0.410 \)). In a logistic regression model, the only predictors of worse functional outcome in NSM patients were higher baseline NIHSS and a proximal occlusion on TCD (\( P<0.05 \)).

Discussion
This study shows that systemic thrombolysis can be safe in terms of intracranial hemorrhage in patients not-fulfilling SITS-MOST criteria. Recanalization and early clinical evolution were comparable. Long-term outcome and mortality tended to be worse in NSM, without reaching statistical significance. If patients older than 80 years were excluded from NSM, functional outcome was similar to SM-patients.

Our protocol was designed to explore safety/efficacy of more flexible criteria in agreement with the existing literature,\(^2\)\(^-\)\(^9\) aiming to increase thrombolysis candidates. It allowed tPA treatment in >50% of our patients.

Main not-fulfilled criteria were age and time-window. Previous studies have suggested safety of tPA in >80 years in terms of SICH, with slightly worse functional outcome and mortality,\(^8\) probably because comorbidity or complications. An exclusion criterion based on previous functional/morbidity state instead of raw age seems more rational.

Our MRI-selected >3 hours patients showed similar SICH and clinical outcomes to <3-hour time-window, in concordance with reports based on ischemic penumbra identification.\(^2\)\(^-\)\(^6\) Parenchymal injury selection rather than preset clock time-window could be considered.

The study has some limitations. Only patients with documented arterial occlusion were included, probably causing our high baseline NIHSS. Our results are thus not extensible to cohorts without vascular-occlusion selection. Furthermore, we did continuous TCD-monitoring; the enhancing effect of ultrasound on thrombolysis\(^1\)\(^0\) could have influenced our data. We did not precalculate the sample size necessary to detect differences, and only included 369 patients. NSM-patients tended to higher mortality and worse long-term outcome, which could reach statistical significance increasing sample size.

This study does not pretend to modify thrombolysis guidelines but to open the debate and promote research.

### Table. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SM-Group n = 169</th>
<th>NSM-Group n = 200</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.9±10</td>
<td>75.1±13</td>
<td>0.000*</td>
</tr>
<tr>
<td>Gender, female</td>
<td>58 (34.3%)</td>
<td>117 (58.5%)</td>
<td>0.000*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>34 (20.2%)</td>
<td>45 (22.6%)</td>
<td>0.336</td>
</tr>
<tr>
<td>Hypertension</td>
<td>86 (51.2%)</td>
<td>123 (62.1%)</td>
<td>0.023*</td>
</tr>
<tr>
<td>Baseline-NIHSS</td>
<td>17 (IQR 8)</td>
<td>16.5 (IQR 9)</td>
<td>0.284</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>130.8±49</td>
<td>137.1±61</td>
<td>0.309</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>152.7±28</td>
<td>154.1±26</td>
<td>0.654</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>82.8±16</td>
<td>81.6±15</td>
<td>0.490</td>
</tr>
<tr>
<td>Platelets</td>
<td>235.9±76</td>
<td>239.7±87</td>
<td>0.679</td>
</tr>
<tr>
<td>INR</td>
<td>1.08±0.1</td>
<td>1.13±0.2</td>
<td>0.004*</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>50 (29.8%)</td>
<td>101 (50.8%)</td>
<td>0.000*</td>
</tr>
<tr>
<td>Tandem occlusion</td>
<td>38 (23.8%)</td>
<td>32 (21.2%)</td>
<td>0.024*</td>
</tr>
<tr>
<td>Stroke subtypes(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>73 (44.2%)</td>
<td>119 (59.8%)</td>
<td>0.019*</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>44 (26.7%)</td>
<td>33 (16.6%)</td>
<td>0.043*</td>
</tr>
<tr>
<td>Undetermined</td>
<td>42 (25.5%)</td>
<td>43 (21.6%)</td>
<td>0.226</td>
</tr>
<tr>
<td>Dissection</td>
<td>6 (3.6%)</td>
<td>4 (2%)</td>
<td>0.346</td>
</tr>
<tr>
<td>Time-to-treatment</td>
<td>141.3±33</td>
<td>209.5±68</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; INR, International Normalized Ratio.
Continuous variables: mean±SD.
Baseline NIHSS: median (interquartile range).
Statistical analysis: 2-tailed Fisher exact test and Pearson \( \chi^2 \) for categorical variables; Student \( t \) test for continuous variables.
*Statistical significance: \( P<0.05 \).

Functional outcome was evaluated by modified Rankin score (mRS) at 3 months (functional independency: mRS \( \leq 2 \)).
Arterial occlusion and recanalization were determined by TCD\(^4\) performed before tPA-bolus and continuously during 2 hours. MRA was used to evaluate arterial occlusion on insufficient temporal windows.

### Neuroimaging Evaluation
Evaluation consisted of: <3 hours (and 40 [32%] patients in the 3 to 6 hours with unavailable MRI), conventional CT-scan criteria\(^a\); 3 to 6 hours, intracranial occlusion+DWI/PWI mismatch >50% on multiparametric-MRI-protocol.\(^2\)
Intracranial hemorrhage was evaluated on 24- to 36-hour CT scan.\(^3\) SICH was defined as "any hemorrhage with any decline in neurological status (NINDS)\(^1\)\(^0\) and "local/remote parenchymal hemorrhage with NIHSS increase \( \geq 4 \) points, or lethal(SITS-MOST)."\(^1\)

### Results
From November 2001 to December 2007, 369 patients (median NIHSS 17, IQR 9; 47.4% women) were included; 169 (45.8%) fulfilled SITS-MOST criteria (SM-group) and 200 (54.2%) not (NSM-group: 91 [45.5%] >80 years, 124 [63.6%] >3-hour time-window, 16 [8.2%] OAC and 12 [6.1%] DM+stroke). Baseline clinical characteristics are shown in the Table.
Multicenter studies comparing tPA/placebo outside SITS-MOST guidelines could help to generalize thrombolysis.

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**Disclosures**
None.

**References**


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