Predictors of Tissue-Type Plasminogen Activator Nonresponders According to Location of Vessel Occlusion

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Background and Purpose—Information on the clinical and hemodynamic profile of intravenous tissue-type plasminogen activator nonresponders, at different locations of arterial occlusion, may improve the selection of candidates for rescue reperfusion therapies. Therefore, we aim to investigate predictors of failing intravenous tissue-type plasminogen activator therapy according to occluded vessel and location of the clot.

Methods—We prospectively evaluated consecutive patients with an acute ischemic stroke admitted within the first 6 hours of onset. Five hundred forty-eight patients with documented intracranial occlusion were included. Patients were categorized according to site of vessel occlusion into 4 distinct groups: proximal middle cerebral artery occlusion (n=251), distal middle cerebral artery occlusion (n=194), internal carotid artery bifurcation occlusion (n=61), and basilar artery occlusion (n=42). Recanalization was assessed on transcranial Doppler at 1 hour of tissue-type plasminogen activator bolus.

Results—Among patients with proximal middle cerebral artery occlusion, the presence of severe extracranial internal carotid artery stenosis or occlusion (OR, 2.36; 95% CI, 1.15–4.84; P=0.02) and age >74 years (OR, 1.84; 95% CI, 1.02–3.31; P=0.04) independently predicted no recanalization. No independent predictors of no recanalization were identified in patients with distal middle cerebral artery occlusion. In patients with internal carotid artery bifurcation occlusion, a previous diagnosis of hypertension (OR, 12.77; 95% CI, 2.12–76.88; P=0.05), and absence of atrial fibrillation (OR, 8.15; 95% CI, 1.40–47.44; P=0.02) emerged as independent predictors of no recanalization. Similarly, among patients with basilar artery occlusion, absence of atrial fibrillation was as an independent predictor of no recanalization (OR, 7.50; 95% CI, 1.40–40.35; P=0.02).

Conclusions—The use of relevant predictors of no recanalization and a rapid neurovascular evaluation may improve the selection of patients for more aggressive rescue strategies. (Stroke. 2012;43:417-421.)

Key Words: acute stroke ■ atrial fibrillation ■ recanalization ■ thrombolysis ■ ultrasonography

The only approved treatment in patients with ischemic stroke presenting within 4.5 hours from symptoms onset is intravenous tissue-type plasminogen activator (IV tPA).1–2 Early artery reopening has been recognized as a surrogate marker of good outcome after tPA therapy.3–4 However, recanalization is achieved in only 30% to 40% of patients and <50% of them become independent at long-term.5 There is evidence that recanalization after IV tPA is influenced by several factors, including time to treatment, size and location of arterial occlusion, atrial fibrillation, and diabetes.6–9 The combined IV tPa and intra-arterial tPA approach to recanalization in patients with ischemic stroke is both feasible and safe and may provide higher recanalization rates than IV tPA alone.10–12 The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial reported on the efficacy of Merci retriever, a device used to reopen occluded vessels in patients ineligible for tPA.13 Multi-MERCI investigators also showed that mechanical thrombectomy is efficacious in opening intracranial vessels of patients who have failed IV tPA and this group of patients may benefit from thrombectomy within 6 hours of stroke onset.14

As such, distinct emerging therapies can now be offered to patients who fail IV tPA. Therefore, it is crucial to clearly and rapidly assess the group of patients that will fail IV tPA treatment and are candidates for more aggressive therapeutic management.

We hypothesized that factors that predict failing IV tPA will differ according to occluded vessel and location of the clot. So, we sought to investigate clinical and hemodynamic predictors of poor response to systemic thrombolysis, namely...
absence of recanalization of the occluded vessel, for distinct cerebral vessels.

Subjects and Methods

Study Population
We prospectively evaluated consecutive patients with an acute ischemic stroke admitted in our hospital within the first 6 hours after symptoms onset. Stroke onset was defined as the last time the patient was known to be without any neurological symptoms. Seven hundred eighteen consecutive patients with a 6-hour nonlacunar ischemic stroke meeting the anterior or posterior cerebral vascular territories were evaluated between March 2001 and April 2011 and treated with IV tPA at the standard dose of 0.9 mg/kg. One hundred seventy patients with an insufficient acoustic temporal window or without initial intracranial occlusion were excluded. Finally, 548 with documented intracranial occlusion were included. The study population was then divided according to site of vessel occlusion into 4 distinct groups: proximal middle cerebral artery (MCA) occlusion (n=251), distal MCA occlusion (n=194), internal carotid artery bifurcation (ICA T) occlusion (n=61), and basilar artery (BA) occlusion (n=42). The local ethics committee approved the study protocol.

Clinical Assessment
Clinical data were prospectively retrieved for each patient including demographic, detailed history of pre-existing vascular risk factors, and medication history.

All patients underwent a standard neurological examination, electrocardiography, blood pressure, and serum glucose levels at admission. Stroke severity at baseline was assessed by the National Institutes of Health Stroke Scale (NIHSS) score.15 All the investigators involved in the clinical assessment were certificated by the National Stroke Association for the use of the NIHSS. Functional outcome was assessed by modified Rankin Scale at 3 months. Good outcome was defined as modified Rankin Scale score ≤2 at 3 months.

Transcranial Doppler and Carotid Ultrasound Protocols
All patients underwent both emergent carotid ultrasound and transcranial Doppler (TCD) to assess site of vessel occlusion and were repeated at 1 hour postthrombolysis for assessment of vessel recanalization. All the carotid ultrasound and TCD studies were done by an attending stroke neurologist with extensive experience and certified in TCD in acute stroke, all of whom have considerable experience in performing sonographic studies.

A standard TCD examination was performed before tPA administration using 1-channel 2-MHz equipment (TCD 100 mol/L, Spencer Technologies, and DWL Multidop ×4). A standard set of diagnostic criteria was applied to diagnose arterial occlusion. Proximal MCA occlusion was defined as the absence of flow or the presence of minimal flow signal throughout the MCA at an insonation depth between 45 to 65 mm accompanied by flow diversion in the ipsilateral anterior cerebral artery and posterior cerebral artery, according to the Thrombolysis In Brain Ischemia grading system.16 Distal MCA occlusion was defined as blunted or dampened signals (Thrombolysis In Brain Ischemia 2 or 3) in the symptomatic artery with <30% flow than the contralateral MCA and flow diversion signs in ipsilateral neighboring arteries. These patterns of occlusion and recanalization on TCD have shown sensitivity and specificity values of >90% against conventional angiography.16 Location of BA occlusion and residual flow signals were determined by the presence of abnormal flow signals also using the Thrombolysis In Brain Ischemia flow grading system.16 Complete occlusion was considered when Thrombolysis In Brain Ischemia grades were 0 to 1.

On admission, all patients underwent emergent carotid ultrasound (5- and 10-MHz linear probes, Aplio-80; Toshiba) examination before tPA administration. The presence and severity of stenosis or occlusion was defined by means of peak systolic velocity and end-diastolic velocity. A severe stenosis (≥70%) presented with peak systolic velocity >230 cm/s and end-diastolic velocity ≥100 cm/s, and a complete occlusion was defined by the absence of flow in the extracranial internal carotid artery.17 Presence or absence of tandem internal carotid artery/MCA (TIM) occlusion was evaluated in the proximal and distal MCA occlusion groups. The presence of TIM occlusion was determined based on previous published criteria.18 Briefly, in the presence of a stenosis ≥70% or occlusion in the extracranial internal carotid artery, TIM required an abnormal wave form (Thrombolysis In Brain Ischemia 0–3) on the ipsilateral MCA associated to collateral flow signals (anterior and posterior communicating arteries, reverse flow in the ipsilateral anterior cerebral artery and ophtalmic artery), flow diversion signs, and compensatory velocity increase (≥20% increase in the contralateral hemispheric vessels or vertebrobasilar arteries).

TCD monitoring of recanalization was conducted during tPA administration and 1 hour after to assess degree of recanalization. A rater using direct visual control of monitoring display determined changes on TCD in each patient. Partial recanalization on TCD was diagnosed when blunted or dampened signals appeared in a previously demonstrated absent or minimal flow. Complete recanalization on TCD was diagnosed if the end-diastolic flow velocity improved to normal or elevated values (normal or stenotic signals).16,19 No change in the abnormal waveforms indicated that no recanalization (NR) had occurred.

CT Scan Protocol
On admission, all patients underwent a CT scan within the first 4.5 hours after stroke onset. CT scans were assessed for the presence of early parenchymal signs of infarct. Also, the proximal MCA and ICA T occlusion groups were checked for hyperdense MCA sign.

Statistical Analysis
Descriptive and frequency statistical analyses were obtained and comparisons were made using IBM SPSS 17.0 software. Statistical significance for intergroup differences was assessed by Pearson χ² or Fisher exact test for categorical variables and by Student t or Mann-Whitney U test for continuous variables. Receiver operating characteristic curves were configured to establish different cutoff points of each continuous variable that optimally predicted NR. Multivariable logistic regression analyses were performed independently to all the groups to determine factors that could be considered as independent predictors of NR. Variables showing P<0.1 in univariate analysis were included in the multivariate model. Also, NIHSS score was included in all the logistic regressions because it was deemed a relevant variable. A probability value of <0.05 was considered significant for all tests.

Results
The main baseline characteristics of the series are summarized in Table 1. Mean age was 71.7±12.4 years (range, 18–97 years). Median NIHSS score on admission was 17 (interquartile range, 11–20). The mean time from symptoms onset to IV tPA administration was 166.7±61 minutes.

On prebolus TCD, 251 patients showed a proximal MCA occlusion, 194 had a distal MCA occlusion, 61 patients had an ICA T occlusion, and 42 had a BA occlusion. Ninety-eight (17.9%) patients had a TIM occlusion.

During the first hour of IV tPA bolus, 186 (33.9%) patients recanalized; 107 (19.5%) had a partial recanalization and 79 (14.4%) a complete recanalization. Recanalization at 1 hour was related to a good outcome at 3 months: 43.1% modified Rankin Scale score ≤2 versus 29.6% modified Rankin Scale score >2 (P=0.002). Ninety-four patients (51.4%) of all that recanalized within 1 hour had <4-point improvement in NIHSS score.
A receiver operating characteristic curve analysis identified age >74 years (sensitivity 58.6% and specificity 63.2%) and a baseline NIHSS score >17 (sensitivity 60% and specificity 48.1%) as cutoff values of age and stroke severity that better predicted NR. In the multivariate logistic regression analysis, the presence of severe internal carotid artery stenosis or occlusion (OR, 2.36; 95% CI, 1.15–4.84; \( P = 0.02 \)) and age >74 years (OR, 1.84; 95% CI, 1.02–3.31; \( P = 0.044 \)) emerged as independent predictors of NR.

**Distal MCA Occlusion**

One hundred ninety-four patients had a distal MCA occlusion. Fifty-eight (29.9%) had recanalized at 1 hour. Of these, 43 (22.2%) had a complete recanalization and 15 (7.7%) had a partial recanalization.

In the univariate analysis, male patients showed a trend toward NR (Table 1). NIHSS score at baseline was comparable between recanalization groups (13 [8–15] for recanalization versus 10 [11–16] for NR; \( P = 0.376 \)). There were also no other significant differences for major vascular risk factors, previous medication, admission blood pressure, baseline CT findings, or serum glucose measure at baseline. In the multivariate logistic regression analysis, no variable (gender or NIHSS score at baseline) appeared as an independent predictor of NR.

**ICA T Occlusion**

From 61 ICA T occlusion patients, 11 (18.0%) had recanalized during the first hour. 3 (4.9%) patients had a complete, and 8 (13.2%) had a partial recanalization. The hyperdense MCA sign was present in 71.4% of the patients who recanalized and in 50.0% of patients who did not recanalize (\( P = 0.036 \)).

### Table 1. Baseline Characteristics and Potential Baseline Factors Associated With Vessel Recanalization or No Recanalization at 1 Hour for Proximal (n=251) and Distal (n=194) MCA Artery Occlusions

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=548)</th>
<th>Recanalization (n=106)</th>
<th>No Recanalization (n=145)</th>
<th>( P )</th>
<th>Recanalization (n=58)</th>
<th>No Recanalization (n=136)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.7±12.4</td>
<td>68.9±13.3</td>
<td>74.7±11.1</td>
<td>0.001*</td>
<td>72.3±12.6</td>
<td>71.0±12.6</td>
<td>0.527</td>
</tr>
<tr>
<td>Gender, male</td>
<td>291 (53.1)</td>
<td>54 (50.9)</td>
<td>64 (44.1)</td>
<td>0.286</td>
<td>39 (67.2)</td>
<td>74 (54.4)</td>
<td>0.097*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>322 (58.8)</td>
<td>62 (58.5)</td>
<td>81 (56.3)</td>
<td>0.723</td>
<td>33 (57.9)</td>
<td>80 (59.7)</td>
<td>0.816</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>115 (21.0)</td>
<td>22 (20.8)</td>
<td>29 (20.1)</td>
<td>0.905</td>
<td>10 (17.5)</td>
<td>29 (21.3)</td>
<td>0.551</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>185 (33.8)</td>
<td>34 (32.1)</td>
<td>48 (33.3)</td>
<td>0.834</td>
<td>18 (31.6)</td>
<td>46 (34.1)</td>
<td>0.738</td>
</tr>
<tr>
<td>Smoking</td>
<td>84 (15.3)</td>
<td>17 (16.2)</td>
<td>19 (13.3)</td>
<td>0.521</td>
<td>10 (17.9)</td>
<td>19 (14.3)</td>
<td>0.534</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>204 (37.2)</td>
<td>47 (44.3)</td>
<td>68 (47.2)</td>
<td>0.651</td>
<td>19 (33.3)</td>
<td>45 (33.1)</td>
<td>0.974</td>
</tr>
<tr>
<td>Coronaryopathy</td>
<td>102 (18.6)</td>
<td>22 (20.8)</td>
<td>21 (14.5)</td>
<td>0.193</td>
<td>10 (17.5)</td>
<td>34 (25)</td>
<td>0.260</td>
</tr>
<tr>
<td>Statin pretreatment</td>
<td>130 (23.7)</td>
<td>23 (22.1)</td>
<td>35 (24.6)</td>
<td>0.644</td>
<td>15 (28.3)</td>
<td>28 (21.5)</td>
<td>0.328</td>
</tr>
<tr>
<td>Hypertension pretreatment</td>
<td>189 (34.5)</td>
<td>30 (30.9)</td>
<td>49 (36.0)</td>
<td>0.417</td>
<td>17 (32.7)</td>
<td>55 (45.8)</td>
<td>0.109</td>
</tr>
<tr>
<td>Antiplatlet pretreatment</td>
<td>208 (38)</td>
<td>39 (37.1)</td>
<td>62 (43.7)</td>
<td>0.303</td>
<td>19 (35.2)</td>
<td>54 (40)</td>
<td>0.539</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>17 (11–20)</td>
<td>18 (14–20)</td>
<td>19 (16–21)</td>
<td>0.057*</td>
<td>13 (8–15)</td>
<td>10 (8–16)</td>
<td>0.376*</td>
</tr>
<tr>
<td>Early signs of infarct in CT</td>
<td>115 (21.0)</td>
<td>30 (42.3)</td>
<td>37 (34.6)</td>
<td>0.301</td>
<td>12 (27.9)</td>
<td>16 (16.3)</td>
<td>0.113</td>
</tr>
<tr>
<td>Hyperdense MCA sign</td>
<td>NA</td>
<td>19 (29.7)</td>
<td>38 (42.7)</td>
<td>0.101</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>152.7±28</td>
<td>150.2±27.2</td>
<td>151.8±26.7</td>
<td>0.656</td>
<td>154.7±25.2</td>
<td>153.4±27.1</td>
<td>0.871</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>82.0±15.5</td>
<td>81.5±14.6</td>
<td>80.3±14.7</td>
<td>0.559</td>
<td>81.2±14.8</td>
<td>84±16</td>
<td>0.336</td>
</tr>
<tr>
<td>Time from symptoms onset to treatment, min</td>
<td>172.1±65.4</td>
<td>167.4±58.8</td>
<td>166.0±57.6</td>
<td>0.995</td>
<td>169.6±52.1</td>
<td>174.7±67</td>
<td>0.794</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>134.5±53</td>
<td>129.3±45.4</td>
<td>140.5±55.3</td>
<td>0.148</td>
<td>122.1±35.2</td>
<td>134.0±62.8</td>
<td>0.202</td>
</tr>
<tr>
<td>Basal internal carotid</td>
<td>98 (17.9)</td>
<td>14 (16.9)</td>
<td>34 (29.8)</td>
<td>0.036*</td>
<td>10 (22.2)</td>
<td>18 (17.8)</td>
<td>0.533</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD, median (interquartile range), or no. (%). MCA indicates middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; SBP, systolic blood pressure; DBP, diastolic blood pressure; NA, not applicable.

*Variables included in the multivariable model (\( P < 0.1 \) and baseline NIHSS score).
As shown in Table 2, a history of hypertension was the only factor associated with NR on univariate analysis (P=0.01). Atrial fibrillation showed a trend toward NR (P=0.067) and was also included in the multivariate analysis.

In the logistic regression analysis, a previous diagnosis of hypertension (OR, 12.77; 95% CI, 2.12–76.88; P=0.01) and absence of atrial fibrillation (OR, 8.15; 95% CI, 1.40–47.44; P=0.022) as factors associated with NR. This observation is in line with previous studies showing that TIM occlusion independently predicted poor outcome. However, in our series, up to 51.4% of patients who recanalized during tPA infusion improved <4 points at 1 hour after treatment. Therefore, the use of clinical improvement as a surrogate marker of ultraearly recanalization seems inaccurate.

The present study demonstrates that baseline clinical and hemodynamic predictors of resistance to 1-hour recanalization after IV tPA vary according to the location of intracranial artery occlusion.

In patients with proximal MCA occlusions, age >74 years and presence of an extracranial internal carotid artery severe stenosis or occlusion were independently associated with lack of recanalization on TCD at 1 hour after tPA infusion. For distal MCA occlusions, there were no variables significantly related to NR in the univariate analysis. In fact, there was only a trend toward NR in males. Unlike patients with proximal MCA occlusion, TIM occlusion was not associated with NR. This observation is in line with previous studies showing that TIM occlusion independently predicted poor response to thrombolysis in patients with proximal but not in those with distal MCA occlusion. In fact, it has been shown that patients with tandem internal carotid artery/distal MCA occlusion exhibited similar recanalization rates as patients with an isolated distal MCA occlusion. Several mechanisms different than clot size may explain the better recanalization profile in patients with TIM lesions with a distal MCA occlusion.
component. Unlike patients with proximal MCA occlusion, the hemodynamic impact of a concomitant cervical carotid stenosis or occlusion may be less relevant in distal MCA clots. In patients with tandem internal carotid artery/distal MCA occlusion, the relative reduction of regional cerebral blood flow in the carotid artery territory may be more effectively compensated through leptomeningeal collateral circulation as compared with patients with TIM lesions with a proximal MCA occlusion component. This may result in a higher pressure gradient to which the clot is exposed and better delivery of tPA to a wider front of recanalization in patients with distal MCA occlusion.

In the ICA T and BA groups, absence of atrial fibrillation was a strong predictor of NR. Previous studies had demonstrated that in IV tPA-treated patients, early recanalization was more frequent, faster, and more complete in patients with cardioembolic stroke. In fact, a cardiac source of emboli was identified in most patients who experienced sudden clot breakup during tPA administration. Previous studies had already focused on the relationship of some these variables and recanalization with tPA. However, to our knowledge, they did not discriminate regarding the occluded vessel or use such an early recanalization time. We chose to investigate NR at 1 hour because it is critical that the assessment of absence of recanalization be early enough to allow rescue endovascular treatment.

This study has certain limitations. First, TCD is an operator-dependent technique. Regarding posterior circulation stroke, the study did not analyze the vertebral or posterior cerebral arteries and focused mainly on the BA. Also, the number of patients studied is comparatively small for complex analyses. The distal MCA group had a number of patients considerably inferior to the proximal group and might not be powered to detect less significant associations as would be expected of distal occlusions. Accordingly, in the multivariable logistic regression analysis focusing on predictors of no recanalization for the ICA T and BA occlusion, the results presented wide CIs and the power to detect associations was limited.

In conclusion, the use of relevant predictors of NR in association with a rapid noninvasive neurovascular evaluation may improve the selection of patients for more aggressive rescue reperfusion strategies. Our main aim should be to develop a score system to identify patients who will fail IV tPA before they start treatment. Such an objective could be pursued by a relatively simple devise of expanding the Safe Implementation of Thrombolysis in Stroke (SITS) database to encompass baseline data on occluded vessel and recanalization at 1 hour.

Disclosures
None.

References
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*Stroke*. 2012;43:417-421; originally published online December 1, 2011;
doi: 10.1161/STROKEAHA.111.632653

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Predicadores de la falta de respuesta al activador tisular del plasminógeno según la localización de la oclusión vascular.

En estudios previos se ha demostrado que la recanalización arterial temprana se asocia con un buen resultado clínico tras la administración intravenosa de activador tisular del plasminógeno (tPA i.v.) en el infarto isquémico agudo. Sin embargo, la recanalización con tPA i.v. se alcanza en un 50% a 60% de los pacientes y, por consiguiente, se han desarrollado tratamientos para mejorar los cuidados para los pacientes en los que fracasa el empleo de tPA i.v. Se ha demostrado que diversos factores, como la carga de coágulo, predican la probabilidad de recanalización arterial. En este estudio prospectivo se investigaron los factores predictivos, clínicos y hemodinámicos de una mala respuesta a la trombólisis intravenosa. La occlusion vascular de arterias grandes se diagnosticó mediante ecografía carotidea y Doppler transcraneal antes de la administración de tPA i.v., y la evaluación de la recanalización se realizó con múltiples exploraciones 1 hora después de la trombólisis. Se incluyó en el estudio a un total de 548 pacientes con oclusión intracraneal, a los que se dividió en 4 grupos: oclusión proximal de la arteria cerebral media (n = 224), oclusión distal de la arteria cerebral media (n = 194), oclusión en T de la arteria carótida interna (n = 61), y oclusión de la arteria basilar (n = 42). Se observó una recanalización durante la primera hora siguiente a la administración del activador tisular del plasminógeno en 185 pacientes (33,9%); en 107 (19,5%) hubo una recanalización parcial y en 70 (14,4%) una recanalización completa. La recanalización se asoció a un buen resultado clínico a los 3 meses (43,1% con una puntuación de la escala de Rankin modificada ≤ 2 frente a 29,6% con una puntuación de la escala de Rankin modificada ≥ 3, p = 0,003). En los pacientes con una oclusión proximal de la arteria cerebral media, la presencia de estenosis grave a oclusión de la arteria cerebral media contralateral y la edad > 74 años fueron factores predictivos independientes para la ausencia de recanalización con el empleo de tPA i.v. En los pacientes con oclusión en T de la arteria carótida interna, los antecedentes de hipertensión y la ausencia de fluctuaciones arteriales fueron factores predictivos independientes para la ausencia de recanalización. En los pacientes con oclusión de la arteria basilar, la ausencia de fluctuaciones arteriales predijo en manera independiente la ausencia de recanalización. Este estudio tiene la limitación de su tamaño muestral y del uso de Doppler transcraneal, una técnica de imagen que depende del operador. Sin embargo, el uso de factores predictivos de la ausencia de recanalización tras la administración de tPA i.v. y la evaluación neurosonográfica rápida puede mejorar la selección de los pacientes para el uso de estrategias de reperfusión más agresivas. Serán necesarios nuevos estudios para evaluar estos resultados. (Comentario al artículo Predictors of Thrombolytic Activator Neureorresponders: According to Location of Vessel Occlusion. Nuno Mendes, David Rodriguez-Luna, Marta Redon, Sandra Benadik-Kier, Marc Fito, Jorge Pagola, Socorro Piqué, Pilar Meier, Jose Alvarez-Sobek, Joan Montserrat, Carlos A. Molina. Stroke. 2013;44:417-421.)