The Argatroban and Tissue-Type Plasminogen Activator Stroke Study
Final Results of a Pilot Safety Study

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Background and Purpose—Argatroban is a direct thrombin inhibitor that safely augments recanalization achieved by tissue-type plasminogen activator (tPA) in animal stroke models. The Argatroban tPA Stroke Study was an open-label, pilot safety study of tPA plus Argatroban in patients with ischemic stroke due to proximal intracranial occlusion.

Methods—During standard-dose intravenous tPA, a 100-µg/kg bolus of Argatroban and infusion for 48 hours was adjusted to a target partial thromboplastin time of 1.75× baseline. The primary outcome was incidence of significant intracerebral hemorrhage defined as either symptomatic intracerebral hemorrhage or Parenchymal Hematoma Type 2. Recanalization was measured at 2 and 24 hours by transcranial Doppler or CT angiography.

Results—Sixty-five patients were enrolled (45% men, mean age 63±14 years, median National Institutes of Health Stroke Scale=13). The median (interquartile range) time tPA to Argatroban bolus was 51 (38–60) minutes. Target anticoagulation was reached at a median (interquartile range) of 3 (2–7) hours. Significant intracerebral hemorrhage occurred in 4 patients (6.2%; 95% CI, 1.7–15.0). Of these, 3 were symptomatic (4.6%; 95% CI, 0.9–12.9). Seven patients (10%) died in the first 7 days. Within the 2-hour monitoring period, transcranial Doppler recanalization (n=47) occurred in 29 (61%) patients: complete in 19 (40%) and partial in another 10 (21%).

Conclusions—The combination of Argatroban and intravenous tPA is potentially safe in patients with moderate neurological deficits due to proximal intracranial arterial occlusions and may produce more complete recanalization than tPA alone. Continued evaluation of this treatment combination is warranted.

Clinical Trial Registration—URL: www.clinicaltrials.gov. Unique identifier: NCT00268762.

Key Words: acute stroke □ anticoagulation □ Argatroban □ thrombin inhibition □ thrombolysis

See editorial, p 623.

The thrombin inhibitor Argatroban (GlaxoSmithKline, Philadelphia, PA) selectively inhibits free and clot-associated thrombin.1,2 Safety has been demonstrated with and without thrombolytics or with aspirin in patients with acute myocardial infarction.3–5 In a randomized trial of Argatroban versus heparin in combination with intravenous thrombolysis for acute myocardial infarction, complete coronary reperfusion was significantly more frequent with Argatroban compared with heparin.6 In animal stroke models, Argatroban safely augments the benefit of recombinant tissue-type plasminogen activator (tPA) by improving microcirculatory flow, increasing speed and completeness of recanalization, and preventing reocclusion.6–10 Argatroban monotherapy (in a double-blind, randomized Phase II trial) in 60 patients with stroke within 48 hours of onset improved...
neurological outcome compared with placebo.\textsuperscript{11} The Argatroban Anticoagulation in Patients with Acute Ischemic Stroke (ARGIS-1) study showed that Argatroban (mean doses of 1.2 and 2.7 µg/kg per minute) monotherapy given within 12 hours of ischemic stroke was safe but no clinical benefit was observed.\textsuperscript{12}

Fifty-seven percent of patients in the National Institute of Neurological Disorders and Stroke rtPA Stroke Study and 58% in the Second European–Australian Cooperative Acute Stroke Study (ECASS-II) failed to show a favorable clinical response to intravenous recombinant tPA monotherapy.\textsuperscript{13–15} The benefit of tPA in acute stroke is linked to the speed and degree of clot lysis and artery recanalization.\textsuperscript{16–18} However, only 20% to 30% of patients will have complete recanalization on transcranial Doppler imaging (TCD) within 2 hours of intravenous tPA therapy, 60% will have only partial recanalization, and 34% of those with any recanalization will experience reocclusion.\textsuperscript{19,20} Because of its short half-life, allowing careful titration of the anticoagulant effect, we hypothesized that Argatroban might be safely added to full-dose intravenous tPA. Furthermore, we hypothesized that the addition of Argatroban to tPA would improve recanalization rates. The first 15 of the current study (total=65) patients were published previously\textsuperscript{21} and the current article focuses on the whole cohort.

Purpose

The primary purpose of this study was to assess the safety of combined Argatroban and tPA in ischemic stroke as measured by the incidence of significant intracerebral hemorrhage (ICH). The secondary objective was to evaluate drug activity by determining the speed and completeness of arterial recanalization and reocclusion.

Methods

Design

The Argatroban tPA Stroke Study was a prospective multicenter, single-arm, open-label, uncontrolled study, which included careful monitoring by an independent physician medical monitor. Because this was the first ever exposure of patients with acute stroke to the combination of tPA and Argatroban, a prespecified group of 15 patients was treated in Phase 1 to obtain a preliminary assessment of safety. If safe, then continued enrollment would occur. Safety was defined as a rate of symptomatic ICH or Parenchymal Hematoma Type 2 intracranial hemorrhage not exceeding 10%. We hypothesized that a hemorrhage rate of 10% might be acceptable only in the setting of significant increases in arterial recanalization, which is highly associated with improved clinical outcomes.

Patient Selection

Inclusion criteria were: (1) age 18 to 85 years; (2) symptom onset within 3 hours (beginning in September 2009, after 27 enrollments, patients receiving tPA up to 4.5 hours were included according to each study site’s treatment protocol);\textsuperscript{22} (3) clot causing complete or partial occlusion by TCD (Thrombolysis in Brain Ischemia [TIBI] flow grades of 0, 1, 2, or 3) or CT angiography (Thrombolysis in Myocardial Infarction flow grade of 0 or 1) before Argatroban infusion in the middle cerebral artery (MCA, M1 [45-65-mm depth] or M2 [<45-mm]), terminal internal carotid artery, posterior cerebral artery (PCA, P1 or proximal P2), distal vertebral artery, or basilar artery. In all cases, the depth of worst TIBI signals on TCD findings was used as the target occlusion; and (4) being eligible by National Institute of Neurological Disorders and Stroke criteria for intravenous tPA treatment.

Exclusions were (1) National Institutes of Health Stroke Scale (NIHSS) level-of-consciousness score ≥2; (2) baseline NIHSS score <5; (3) baseline NIHSS score >17 (modified to >15 after the first 15 patients) for right hemisphere and ≥22 (modified to >20) for left hemisphere strokes; (4) pre-existing modified Rankin Scale (mRS) score ≥2; (5) history of ICH or significant bleeding within 3 months; (6) hypotension ≥2/3 of the MCA territory on CT; (7) coagulopathy or clinically significant bleeding; (8) international normalized ratio >1.5; (9) major surgery within 6 weeks or anticipated surgery within the next 7 days; (10) significant liver disease; (11) brain tumor; (12) severe organic brain disorder; (13) stroke, myocardial infarction, pericardiitis, intracranial surgery, or significant head trauma within 3 months; (14) prestroke life expectancy <3 months; and (15) need for concomitant use of anticoagulants other than Argatroban.

All informed consent from the patient, family, or legal representative and before starting Argatroban, all patients had routine admission laboratory tests, TCD (CT angiography in patients without temporal windows or lack of TCD availability), NIHSS, and mRS. All patients received intravenous tPA (0.9 mg/kg). There was no delay in starting intravenous tPA as a result of participation in this study. Informed consent and other qualifying activities for the study took place after the intravenous recombinant tPA bolus was given. Argatroban as a 100-µg/kg bolus over 3 to 5 minutes was administered intravenously within 1 hour of the tPA bolus followed by a continuous Argatroban infusion of 1.0 µg/kg per minute for 48 hours adjusted to a target activated partial thromboplastin time of 1.75± baseline (±10%). The Argatroban infusion rate was adjusted in response to the activated partial thromboplastin time according to a dosing algorithm 2, 6, 12, and 24 hours after initiation of Argatroban; at the end of Argatroban infusion; within 2 to 4 hours of any dose adjustment; and in the event of a major bleed in which case the infusion was terminated immediately.

Concomitant anticoagulants or antiplatelet agents were not permitted during Argatroban. CT was performed at baseline, 48 hours after the intravenous recombinant tPA bolus, and for any increase in NIHSS score of ≥2 points more than baseline. CT scans demonstrating any ICH were reviewed (along with a clinical summary) by an independent physician safety monitor. NIHSS scores were measured at 2, 24, and 48 hours after tPA bolus and for clinical worsening. mRS, Barthel Index, and Glasgow Outcome Scale scores were obtained 48 hours and 7 days after tPA bolus. Ninety-day mRS scores were obtained if part of routine follow-up care.

Vessel Imaging

Patients were eligible for enrollment through either a TCD or CT angiographic pathway. The TCD pathway mandated a diagnostic TCD to confirm vessel occlusion. Repeat assessments (<1 minute of ultrasound exposure) were performed at the start of Argatroban infusion and at 30, 60, 90, and 120 minutes and 24 and 48 hours after tPA bolus. All TCD studies were carried out by a certified technologist. Arterial recanalization was graded by the previously validated TIBI system.\textsuperscript{17} TCD criteria had been previously validated against CT angiography.\textsuperscript{23} TCD and CT angiography studies were reviewed and adjudicated by central readers (Z.G., R.M., and A.M.D.) who were unaware of the patients’ clinical course. In MCA strokes, recanalization and reocclusion were determined from the most proximal portion of the MCA with the lowest qualifying TIBI score. If flow was absent in a segment, the immediately proximal segment was used. If TIBI was 3 in all segments, the most distal segment was used. Recanalization was defined as an increase in TIBI by ≥1 grade compared with baseline and an overall TIBI ≥2. Partial recanalization was improvement to Grade 2 or 3, and complete recanalization was improvement to Grade 4 or 5. Reocclusion was worsening of TIBI by ≥1 grade (whether or not recanalization had occurred) with the following exceptions: TIBI 2 or 3 had to decrease to TIBI Grade ≤1 and TIBI 4 or 5 had to decrease to TIBI ≤3.

Patients enrolled through the CT angiography pathway underwent a pretreatment CT angiogram using each site’s standard helical CT
scanner technology. Postprocessing of the images into 2-dimensional and 3-dimensional projections was obtained per local protocols. Intracranial arterial occlusions of the proximal vessels were eligible (Thrombolysis in Myocardial Infarction ≤1). Follow-up CT angiograms were mandated at 24 hours; partial recanalization was improvement to Thrombolysis in Myocardial Infarction 2 and complete to Thrombolysis in Myocardial Infarction 3.

Safety Monitoring and Statistical Considerations
This study was approved by each participating institution’s Committee for the Protection of Human Subjects and an independent data and safety monitoring committee provided safety oversight. The primary outcome, significant ICH, was defined as either symptomatic or Parenchymal Hematoma Type 2 (PH-2). Symptomatic ICH was defined as ICH present on cerebral CT temporally related to a decline in neurological status in the judgment of the clinical investigator. PH-2 was confluent bleeding occupying >30% of the infarct volume and causing a significant mass effect.24

Major systemic bleeding was any bleeding associated with a fall in hemoglobin of ≥2 g/dL or resulting in a blood transfusion. A prospective stopping rule mandated enrollment cessation if >2 significant hemorrhages occurred in the first 15 patients. The results of the first 15 patients were compiled, analyzed, and sent to the Food and Drug Administration.21 At their request, because of 2 ICHs in the first 15 patients, the sample size was increased to 65, and we agreed on the following stopping rules: Using an asymmetrical group sequential method, stopping rules were calculated for every additional group of 5 patients that mandated enrollment cessation if the lower limit of 80% CI for significant hemorrhage rate exceeded 10% or the upper limit of 90% CI was <10%. Analyses were conducted using SAS Version 9.2 (Cary, NC).

Results
From May 2003 through August 2010, 65 patients (29 men) were enrolled. Although it was originally intended to complete the study over 5 years, regulatory issues before recruitment and during interim safety reviews meant that recruitment did not occur between Years 2 and 3; additionally, time-limited funding further slowed the recruitment rate. Ninety-percent of patients had MCA occlusions (66% M1, 34% M2). Median baseline NIHSS score was 13 (range, 3–25; Table 1). Median time from symptom onset to tPA bolus was 128 (interquartile range, 94–170) minutes. Table 2 and the Figure describe the anticoagulation response as well as Argatroban infusion results. Fifty-eight patients (89%) started the Argatroban before the end of the tPA infusion, whereas 7 (11%) experienced a delay of 14 ± 13 minutes. One patient received only the Argatroban bolus without the infusion due to suspected (but not subsequently confirmed) hemorrhagic transformation. Thirty-one (48%) of 65 patients reached or exceeded target activated partial thromboplastin time within 2 hours.

Safety Outcomes
Table 3 details the safety results. Significant ICH occurred in 4 (6.2%) of 65 patients (95% CI, 1.7–15). Of these, 3 were symptomatic (4.6%; 95% CI, 0.9–12.9). Two PH-2 hematomas occurred (3.1%; 95% CI, 0.4–10.7); 1 patient experienced a PH-2 that was also symptomatic. All cases of significant ICH occurred in the setting of a large territorial infarction.

The first 2 significant hemorrhages occurred with NIHSS scores of 15 and 21 (both right MCA strokes), prompting the data and safety monitoring board to reduce the upper limit of the NIHSS score to 15 (right hemisphere) and 20 (left hemisphere). The 4 hemorrhages occurred 26, 19, 3.5, and 23 hours after tPA treatment. The highest partial thromboplastin time values for these patients were 61.3, 43.5, 59.7, and 32.7. A total of 32 serious adverse events occurred in 22 patients (see Table 3).

Clinical and Recanalization Outcomes
At 7 days, there was a median decrease (improvement) in NIHSS scores from baseline by 8 points (P<0.001). Also at
Day 7 or discharge, 29% had a mRS of 0 or 1, the median Barthel Index was 55 (interquartile range, 17.5–92.5), and the median Glasgow Outcome Scale was 4 (interquartile range, 3–5). On discharge, 76% of patients went either home or to acute rehabilitation, and 7 patients died (10.8%). Five of the 7 deaths resulted from large hemispheric infarction with herniation, whereas the other 2 died from respiratory failure. Six of the 7 deaths occurred after the family requested withdraw of care. At 90 days, data were available from 50 patients: 18 patients (36%) experienced a mRS of 0 or 1; 5 were mRS of 2 (10%); 4 were mRS of 3 (8%); 13 were mRS of 4 (26%); 2 were mRS of 5 (4%); and 8 patients were dead (16%).

The distribution of qualifying lesions on TCD and CT angiography are in Table 1. Six non-MCA cases were included (5 terminal internal carotid artery and 1 vertebral artery occlusion). Of the 59 MCA occlusions, 39 (66%) were M1 and 20 (34%) M2 segments. Recanalization adjudication was performed on all patients except for 5 cases in which images were unavailable. In these 5, the local assessment of recanalization was used for analysis (1 complete recanalization, 2 partial recanalizations, and 2 without recanalization). Of the 60 adjudicated cases, there was agreement in 57 (95%) between the local interpretation and the blinded rater. All TCD cases were in agreement. Three CT angiography cases underwent additional review and agreement was obtained after further discussion between the principal investigator and the blinded assessor. Within the 2-hour monitoring period, TCD recanalization occurred in 29 of 47 (61%) patients:

### Table 2. PTT and Argatroban Infusion Results, Median (IQR)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minutes from tPA bolus to Argatroban bolus</td>
<td>51 (38–60)</td>
</tr>
<tr>
<td>Minutes of tPA-Argatroban overlap</td>
<td>17 (4–26)</td>
</tr>
<tr>
<td>Hours to (or above) target aPTT</td>
<td>3 (2–7)</td>
</tr>
<tr>
<td>Hours of Argatroban infusion</td>
<td>48 (7–48)</td>
</tr>
<tr>
<td>Hours at (or above) target aPTT</td>
<td>25 (19–33)</td>
</tr>
<tr>
<td>No. of Argatroban infusion adjustments</td>
<td>6 (5–8)</td>
</tr>
<tr>
<td>First aPTT after Argatroban bolus (seconds)</td>
<td>45 (41–72)</td>
</tr>
<tr>
<td>Range</td>
<td>(25–149)</td>
</tr>
</tbody>
</table>

PTT indicates partial thromboplastin time; IQR, interquartile range; tPA, tissue-type plasminogen activator; aPTT, activated partial thromboplastin time.

complete in 19 (40%) and partial in 10 (21%; Table 4). Six (12.7%) patients recocluded after earlier complete or partial recanalization. Sixty patients had vessel imaging at 24 hours demonstrating complete recanalization in 63% (n=38) and partial in 15% (n=9; total 78% any recanalization).

### Table 3. Safety and Bleeding Results

<table>
<thead>
<tr>
<th>Event</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant intracranial hemorrhage</td>
<td>4 (6.2, 1.7–15)</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>3 (4.6, 0.9–12.9)</td>
</tr>
<tr>
<td>Parenchymal hematoma Type 2*</td>
<td>2 (3.1, 0.4–10.7)</td>
</tr>
<tr>
<td>Asymptomatic intracranial hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Parenchymal hematoma Type 1</td>
<td>3 (4.6, 1–12.9)</td>
</tr>
<tr>
<td>Hemorrhagic transformation Type 2</td>
<td>4 (6.2, 1.7–15.0)</td>
</tr>
<tr>
<td>Hemorrhagic transformation Type 1</td>
<td>8 (12, 5.5–22.8)</td>
</tr>
<tr>
<td>Total</td>
<td>15 (23, 13.5–35.2)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ICH, intracerebral hemorrhage.

*One patient had a parenchymal hemorrhage Type 2 that was also symptomatic.
†One patient had elevation in creatinine and liver function tests due to decreased cardiac output and 1 patient had severe hypokalemia.

**Figure.** Partial thromboplastin time (PTT) values: baseline (pre-tPA), 2, 6, 12, 24 and 48 hours. Target activated partial thromboplastin time (aPTT) is displayed as the horizontal bar. tPA indicates tissue-type plasminogen activator.
Of all patients who had TCD data at 2 hours or CT angiography patients who had 24-hour recanalization data available (n=63), more patients who had either complete or partial recanalization experienced a mRS of 0 or 1 at day 7 compared with nonrecanalizers (44% versus 30%, P=0.336). Proximal clot location experienced higher rates of complete or partial recanalization compared with distally located thrombi (69% versus 38%, P=0.019). However, of the 5 terminal internal carotid artery occlusions, 3 failed to recanalize and 2 partially recanalized.

**Discussion**

Current guidelines do not allow antiplatelets, antithrombotics, or anticoagulants until after 24 hours from thrombolysis. Despite the limited sample size, our study provides preliminary evidence that anticoagulation with Argatroban during this timeframe appears safe. The 95% CI for ICH was 0.9 to 12.9, for PH-2 it was 0.4 to 10.7, and for either it was 1.7 to 15.0. At no time during the study were we ≥80% certain that the true rate of either ICH or PH-2 exceeded 10%. These rates of bleeding are of the same order of magnitude seen with intravenous recombinant tPA alone and therefore low enough to justify further evaluation in more patients to arrive at a more confident assessment of the true risks of bleeding. Argatroban was chosen because it has been shown to increase the speed and completeness of recanalization at the same time as improving flow in the microcirculation. In addition, safety has been demonstrated in combination with tPA in both experimental models and clinical cardiac trials. Platelet glycoprotein IIb/IIa antagonists or other antithrombotic agents might also be used advantageously in combination with tPA. An advantage of Argatroban is its short half-life, which allows rapid offset of action in case of bleeding and the ease of monitoring its antithrombotic effect by the activated partial thromboplastin time. Thrombin inhibition also prevents injury to vascular endothelium, thus facilitating endogenous plasminogen activator production. We chose the Argatroban dose based on 2 considerations. We wanted to give standard-dose tPA so that patients would not be deprived of proven effective therapy. We started with a low-dose algorithm of Argatroban because in previous trials, it was safe. Higher doses of Argatroban might also be safe and even more effective, but this will require careful evaluation.

The 48-hour duration of treatment was chosen because it was used in previous studies and we wanted to be sure to treat long enough to prevent any reocclusion. However, 3 of our 4 significant hemorrhages occurred >18 hours into the infusion. A 12- to 18-hour infusion might produce even safer and equally effective results.

The rate of ICH and PH-2 in this study approximates a comparable cohort of patients and historical data. Because the NIHSS score predicts bleeding risk from tPA, we put a ceiling on admission NIHSS score after our first 2 hemorrhages. Subsequent studies might explore if such limits are necessary.

Although an overall effective treatment for ischemic stroke, intravenous tPA is less efficacious for larger, more proximal occlusions. Only 4.4% of distal internal carotid artery and 30% to 32% of MCA clots recanalize. In addition, reocclusion causes neurological deterioration, higher in-hospital mortality, and is likely related to the short treatment effect of tPA. There exists an urgent need for safe amplification of tPA reperfusion that can be universally available and performed in any emergency department setting. Our goal was to safely achieve immediate and complete recanalization quickly after tPA treatment. Based on our previous experience, we think that our high rate of complete or partial recanalization (55%) at 2 hours after tPA treatment may be better than tPA alone and as useful as any other intervention currently available, particularly considering the potential widespread applicability of this combined pharmacological approach.

**Limitations**

Study limitations include possible selection bias and investigators unblinded to treatment. However, these design characteristics are typical of pilot safety analyses evaluating first human exposure to a particular treatment that may have high risks. Furthermore, by appointing an independent monitor to adjudicate all hemorrhagic events, we have minimized these limitations. In addition, although 60 of 65 patients had 24-hour recanalization data, only 47 were available at 2 hours.

**Conclusions**

Argatroban in combination with intravenous tPA appears potentially safe in patients with moderate neurological deficits due to proximal intracranial arterial occlusions and may produce more complete recanalization compared with tPA alone. Further study of this treatment combination appears warranted.

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Data Safety and Monitoring Board: David Chiu, MD, Debra J. del Junco, PhD, S. Chris Pappas, MD, Igor Cherches, MD, and Thomas A. Kent.

Independent Physician Safety Monitor: Pitchaiah Mandava, MD.

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Disclosures
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References
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Argatroban and Tissue-Type Plasminogen Activator Stroke 研究 — 安全性に関するパイロット研究の最終結果

The Argatroban and Tissue-Type Plasminogen Activator Stroke Study — Final Results of a Pilot Safety Study

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表3 安全性および出血に関する結果

| 重大な頭蓋内出血 例数（％、95％CI） | 4 (6.2、1.7～15) |
| 症候性ICH 例数（％、95％CI） | 3 (4.6、0.9～12.9) |
| 脳実質内血腫2型* 例数（％、95％CI） | 2 (3.1、0.4～10.7) |
| 脳実質内血腫1型 例数（％、95％CI） | 3 (4.6、1.2～12.9) |
| 出血性変化2型 例数（％、95％CI） | 4 (6.2、1.7～15.0) |
| 出血性変化1型 例数（％、95％CI） | 8 (12.5、22.8) |
| 合計 例数（％、95％CI） | 15 (23.1、35.2) |
| * 1例には症候性の脳実質内出血2型が認められた。
| † 1例に心拍出量減少に起因するクレアチニン値変動および肝機能検査値上昇が認められ、1例に重度低カリウム血症が認められた。|

CI：信頼区間、ICH：脳内出血。

結論：アルガトロンとt-PA静注の併用は、頭蓋内動脈近位部閉塞による中等度の神経脱落徴候のある患者に安全に用いることが可能であり、t-PA単独の場合よりも完全な再開通が得られることが多いと思われる。今後も継続的な評価が必要である。

臨床試験登録：URL：www.clinicaltrials.gov 固有識別番号：NCT00268762。
El estudio Argatroban and Tissue Plasminogen Activator Stroke Study: resultados finales de un estudio piloto de seguridad

Con la excepción de una ampliación de la ventana terapéutica en determinados pacientes seleccionados, poco ha cambiado en el tratamiento trombolítico del ictus agudo desde la introducción del activador tisular del plasminógeno recombiente por vía intravenosa. En este número de Stroke, Barrere y colaboradores presentan los resultados del Argatroban Tissue Plasminogen Activator Stroke Study, el que se investigó si la adición de argatroban al activador tisular del plasminógeno en las primeras 4,5 horas podía mejorar de forma segura las tasas de revascularización en los pacientes con occlusiones de arterias grandes (arteria cerebral media, arteria caudada interna terminal, arteria cerebral posterior, arteria vertebral distal o arteria basilar) según lo determinado mediante Doppler transcraneal o angio-TC. Todos los pacientes recibieron tratamiento intravenoso con activador tisular del plasminógeno recombiente (0,9 mg/kg). Argatroban, en un bolso de 100 μg/kg a lo largo de 3 a 5 minutos se administró por vía intravenosa en el plano de 1 hora tras la administración de un bolso de activador tisular del plasminógeno recombiente, seguido de una infusión continua de argatroban de 1,0 μg/kg por minuto durante 48 horas, ajustada para alcanzar un objetivo de tiempo de tromboplastina parcial activada de 1,75 x valor basal. La variable de valoración primaria de la seguridad fue la tasa de hemorragia intracraneal sintomática definida por la presencia de hemorragia intracraneal en la TC cerebral asociada a un deterioro neurológico o hemorragia parenquimatosa de tipo 2. Se evaluó el grupo según los grados de Thrombolysis in Brain Ischemia (Doppler transcraneal) o de Tissueplasminogen Activator Stroke Study (angio-TC). Se incluyó en el estudio a 61 pacientes a lo largo de un periodo de 7 años. La tasa de hemorragias intracraneales sintomáticas, resultado aceptable (4,6%), y se produjo una revascularización completa en un 30% de los casos a las 2 horas (Doppler transcraneal) y en un 62% a las 24 horas (angio-TC). La puntuación de la National Institute of Health Stroke Scale mejoró en una mediana de 8 puntos a los 7 días. Aunque el 20% de los pacientes presentaron una evolución clínica excelente (escala de Rankin modificada 0-1), la mortalidad fue del 11%. Los autores llegaron a la conclusión de que el tratamiento combinado utilizado puede ser seguro en pacientes con déficit neurológicos moderados. El estudio tiene ciertas limitaciones: la más evidente es la falta de un grupo control apropiado. Sin embargo, subraya la necesidad de contener con pruebas de eficacias terapéuticas sustanciales cuando puedan comportar un riesgo adicional, sobre todo si los datos pronósticos y la información obtenida en situaciones clínicas similares sugieren un posible beneficio beneficioso. (Comentario al artículo The Argatroban and Tissue-Type Plasminogen Activator Stroke Study; Final Result of a Pilot Safety Study, Andrew D. Barrere, Andre V. Alexandrov, Pat Lyden, Jessica Lee, Sheryl Martin-Schild, Lorea Shieh, Tingting Wu, April Sisson, Kennguyaki Panturraga, Zhengyu Chen, Mohammad H. Rabie, Gudule Babazadeh, Kristian Eulein, Rebecca M. Oggy, Zsolt Grami, Georgios Tzogias, Nicole R. Gonzales, Sam I. Savitz, Robert Malek, Andrew M. Demchuk and James C. Grotta Stroke 2012;46:776-775.)