Argatroban Anticoagulation in Patients With Acute Ischemic Stroke (ARGIS-1)

A Randomized, Placebo-Controlled Safety Study

Marian P. LaMonte, MD, MSN; Marshall L. Nash, MD; David Z. Wang, DO; Andrew R. Woolfenden, MD; John Schultz, PhD; Marcie J. Hursting, PhD; Philip M. Brown, MD, JD; for the ARGIS-1 Investigators

Background and Purpose—Direct thrombin inhibitors, including argatroban, represent an anticoagulant class distinct from heparins. We investigated the safety of 2 levels of argatroban anticoagulation in acute ischemic stroke.

Methods—This multicenter, randomized, double-blinded, placebo-controlled study included 171 patients with acute (≤12 hours from onset) stroke and National Institutes of Health Stroke Scale (NIHSS) scores of 5 to 22. Patients received continuous intravenous argatroban (100 μg/kg bolus) at 3 μg/kg per minute (n=59) or 1 μg/kg per minute (n=58), respectively, adjusted to target activated partial thromboplastin times (aPTTs) 2.25× and 1.75× baseline or placebo (n=54) for 5 days. The primary outcome was symptomatic intracranial hemorrhage (ICH) at 30 days.

Results—Baseline characteristics including neurologic deficits (median NIHSS score 9) were comparable between groups. Argatroban at mean doses of 2.7 and 1.2 μg/kg per minute increased aPTTs significantly (P<0.001), with mean aPTTs at or near target values throughout infusion. Symptomatic ICH was not significantly different between groups (high-dose argatroban, 5.1%; low-dose argatroban, 3.4%; placebo, 0%; P=0.18), with 3 events during argatroban infusion and 2 events ≥7 days after stopping infusion. No significant between-group differences occurred in asymptomatic ICH (7 events), major systemic hemorrhage (no event), or 90-day mortality (13.4% overall).

Conclusions—In this first North American randomized, double-blinded, placebo-controlled study of direct thrombin inhibition in acute ischemic stroke, argatroban at each dose evaluated significantly prolonged aPTTs without increasing ICH or major bleeding. These results suggest that argatroban provides safe anticoagulation in acute ischemic stroke, warranting future studies powered to evaluate its efficacy and more precisely estimate event rates. (Stroke. 2004;35: 1677-1682.)

Key Words: stroke, acute thrombin, antagonists and inhibitors randomized controlled trials anticoagulant agents

Urgent routine anticoagulation with heparin, low-molecular-weight heparins, or heparinoid is not recommended in acute ischemic stroke (AIS).1 These agents increase bleeding complications, eg, intracranial hemorrhage (ICH), without increasing favorable outcomes except perhaps in large-artery atherosclerotic stroke.1 Other limitations of heparins are unpredictable anticoagulant effects, dependence on adequate antithrombin levels, no inhibition of clot-bound thrombin, and heparin-induced thrombocytopenia (HIT).2 Direct thrombin inhibitors including argatroban represent an anticoagulant class distinct from heparins (and thrombolytic and antiplatelet agents) and have not been prospectively studied outside Japan for treating AIS.

Argatroban directly inhibits free and clot-bound thrombin and, hence, thrombin-induced activities, eg, platelet aggregation and endothelin-1 release.3 Argatroban has predictable anticoagulant effects,4 does not induce or potentiate HIT,5 causes less bleeding compared with heparin for the same anticoagulant effect,6 and is well-tolerated in various settings.7–11 Preclinical12–16 and clinical11,17 studies indicate that argatroban offers benefits in AIS. In rat models, argatroban increases blood flow to the penumbral area and reduces infarct size, microthrombi counts, and neurologic deficit.12,13 Researchers postulate that argatroban, by inhibiting thrombin formed locally in response to ischemia, prevents subsequent microthrombi formation, improves blood flow to the peri-ischemic areas, and thus rescues at-risk neuronal cells.16 In a double-blinded, placebo-controlled Japanese study, intravenous argatroban (60 mg/d for 2 days, then 10 mg twice daily for 5 days) significantly improved global outcome in patients...
treated within 48 hours of stroke, without increasing ICH. In a casebook review of 2 historical controlled studies, which included 960 patients, argatroban (mean doses, 1.7 to 2.0 μg/kg per minute) reduced new stroke and stroke-associated mortality in HIT, without increasing ICH or major bleeding. Among other uses, argatroban is available as an anticoagulant in Japan for treating large-artery atherosclerotic stroke and in America for prophylaxis or treatment of thrombosis in HIT and during percutaneous coronary interventions in patients with or at risk for HIT.

Few randomized, controlled studies of intravenous anticoagulation in AIS are reported. We report a North American randomized, double-blinded, placebo-controlled study to establish safety and explore outcomes of 2 levels of intravenous argatroban in patients treated within 12 hours of AIS symptom onset.

**Materials and Methods**

This multicenter, randomized, double-blinded, phase 2, placebo-controlled study of argatroban in ischemic stroke (ARGIS-1) was conducted between April 2001 and August 2002 at 42 North American centers. Each center’s institutional review board approved the study. Subjects gave informed consent.

**Patients**

Males and nonpregnant females, aged 18 to 85 years, presenting within 12 hours of AIS symptom onset with a National Institutes of Health Stroke Scale (NIHSS) score of 5 to 22 were eligible. Patients within 12 hours of AIS symptom onset with a National Institutes of Health Stroke Scale (NIHSS) motor component of ≥1 point in NIHSS level of consciousness component within 30 days. Secondary safety outcomes were major systemic hemorrhage (ie, bleeding into a major prostatic joint; retroperitoneal bleeding; or other major hemorrhage associated with a hemoglobin decrease ≥2 g/dL and blood transfusion ≥2 U), asymptomatic ICH (ie, parenchymal hemorrhage, hemorrhagic infarction, or hemorrhagic transformation detected by CT but without meeting score criteria for symptomatic ICH), and minor systemic bleeding (ie, bleeding not meeting criteria for major systemic hemorrhage) within 30 days.

Although the study sample size was insufficient for a statistically robust efficacy analysis, we explored patient outcomes by group. Randomized patients without significant protocol or entry criteria violations who received drug infusion ≥2 days (no gap >4 hours) were prespecified as the efficacy population for exploration of outcomes. Outcomes included the NIHSS, mRS, and Barthel index (BI) assessed at baseline (NIHSS and mRS only), daily during treatment (NIHSS only), and at discharge/early withdrawal, 30 days, and 90 days by personnel blinded to the patient’s treatment assignment and aPTTs. Baseline mRS scores reflected conditions before the qualifying stroke. Stroke severity scores at 90 days were dichotomized as “success” (ie, NIHSS score 0 to 1 or 40% improvement over baseline; NIHSS score 0 to 1; mRS score 0 to 2; or BI score ≥85) or “failure” (including death). Worse possible scores were given on patient death.

**Safety Oversight**

An independent Data and Safety Monitoring Board provided safety oversight. As support for their oversight, an independent neuroradiologist performed centralized, blinded review of CT scans on patients who experienced neurologic deterioration or serious adverse events related to neurologic bleeding and whose complete films were available (n=60). Centralized and local reviews agreed regarding bleeding, except for 1 patient (low-dose argatroban) with ICH by local, yet not centralized, review; 1 patient (high-dose argatroban) with ICH by centralized review and “suggestion of petechial bleeding” by local review; and 3 patients (each active treatment) with minimal/peuticeal bleeding by centralized, yet not local, review.

**Statistical Methods**

One hundred eighty subjects, 60 per group, were planned. In the primary safety analysis, with 120 subjects administered study drug, there was a 95% chance of observing a drug-related event with a true occurrence rate of 2.5%. Regarding comparisons between placebo and the combined active treatment groups, a difference in event rate of ~10% could be detected with 80% power using a 2-sided test at the 0.05 level. Tests of interactions and baseline differences were 2-sided at a 0.10 significance level; other tests were 2-sided at a 0.05 significance level. No adjustments were made for multiple comparisons. Comparisons were made between active treatment groups.
Efficacy population 47 (80) 39 (67) 47 (87)
Completed study 48 (81) 45 (78) 47 (87)
Safety population† 59 58* 54

For demographic and baseline characteristics, continuous variables were analyzed using analysis of variance, adjusting for treatment, with baseline aPTT as covariate.

Categorical variables were analyzed using the Kruskal–Wallis test (smoking and alcohol history) or Cochran–Mantel–Haenszel general association test. Changes in aPTT were analyzed using analysis of covariance, adjusting for treatment, with baseline aPTT as covariate.

Results

Patients
In the safety population, 171 patients received high-dose (n=59) or low-dose (n=58) argatroban (respectively adjusted to achieve aPTTs 2.25× and 1.75× baseline), or placebo (n=54) within 12 hours of AIS symptom onset (Table 1). One hundred forty (82%) patients completed the study. The efficacy population included 133 patients.

In the safety population, the groups were similar regarding demographic and baseline characteristics, except age and alcohol use (Table 2). Vital signs and routine laboratory values were similar between groups (data not shown), except serum glucose (range of group means: 6.4 to 7.8 mmol/L; P=0.051) and aPTT (26.8 to 28.8 seconds; P=0.032). Overall, the median NIHSS score was 9. The mean time from symptom onset to treatment was 9 hours (SD: 2) in each group. In the efficacy population, INR (range of group means: 0.99 to 1.04; P=0.08), age, alcohol use, serum glucose, and aPTT demonstrated significant between-group differences and were covariates in exploration of patient outcomes.

Dosing
All patients received an initial bolus. Mean (SD) infusion doses were 2.7 (0.9) and 1.2 (0.5) μg/kg per minute, respectively, for high-dose and low-dose argatroban. Argatroban versus placebo significantly prolonged aPTTs within 2 hours of starting therapy (P<0.001, each group). Mean aPTTs were compared using the log-rank test.

Exploration of patient outcomes was conducted using the prespecified efficacy population. Logistic regression analyses were performed on dichotomized outcomes, numerical scores at discharge/early withdrawal and at 90 days, and serial NIHSS scores. Covariates used in the analyses were demographic or baseline characteristics that demonstrated between-group differences (0.10 significance level), baseline neurologic scores, and time from symptom onset to treatment.

Safety analyses were conducted on the prespecified safety population. Bleeding and adverse event rates were compared between groups using Fisher’s exact test. Seven- and 90-day mortality was summarized by group. Kaplan–Meier estimates of 90-day survival were compared using the log-rank test.

TABLE 1. Demographic and Baseline Characteristics (Safety Population)

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>High-Dose Argatroban (N=59)</th>
<th>Low-Dose Argatroban (N=58)</th>
<th>Placebo (N=54)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>70±13</td>
<td>70±12</td>
<td>65±13</td>
<td>0.038</td>
</tr>
<tr>
<td>Weight, kg*</td>
<td>80±18</td>
<td>79±16</td>
<td>78±20</td>
<td>0.90</td>
</tr>
<tr>
<td>Female</td>
<td>31 (53)</td>
<td>37 (64)</td>
<td>31 (57)</td>
<td>0.47</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>10 (17)</td>
<td>10 (17)</td>
<td>9 (17)</td>
<td>0.50</td>
</tr>
<tr>
<td>White</td>
<td>48 (81)</td>
<td>47 (81)</td>
<td>42 (78)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>13 (22)</td>
<td>13 (22)</td>
<td>17 (32)</td>
<td>0.28</td>
</tr>
<tr>
<td>Current drinker</td>
<td>11 (19)</td>
<td>17 (29)</td>
<td>19 (35)</td>
<td>0.07</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>15 (25)</td>
<td>14 (24)</td>
<td>10 (19)</td>
<td>0.23</td>
</tr>
<tr>
<td>Qualifying stroke type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>18 (35)</td>
<td>14 (29)</td>
<td>11 (22)</td>
<td>0.65</td>
</tr>
<tr>
<td>Small-artery occlusion</td>
<td>15 (29)</td>
<td>15 (31)</td>
<td>18 (35)</td>
<td></td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>8 (16)</td>
<td>12 (24)</td>
<td>8 (16)</td>
<td></td>
</tr>
<tr>
<td>Other cause</td>
<td>4 (8)</td>
<td>1 (2)</td>
<td>7 (14)</td>
<td></td>
</tr>
<tr>
<td>Multiple causes</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Undetermined cause</td>
<td>5 (10)</td>
<td>6 (12)</td>
<td>6 (12)</td>
<td></td>
</tr>
<tr>
<td>NIHSS score, median (range)</td>
<td>9 (5–22)</td>
<td>10 (5–22)</td>
<td>9 (5–20)</td>
<td>0.29</td>
</tr>
<tr>
<td>Symptom onset to treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3–6 hours</td>
<td>12 (20)</td>
<td>10 (17)</td>
<td>9 (17)</td>
<td>0.69</td>
</tr>
<tr>
<td>&gt;6–12 hours</td>
<td>46† (78)</td>
<td>48 (83)</td>
<td>45 (83)</td>
<td></td>
</tr>
</tbody>
</table>

Mean (SD) absolute aPTT change versus baseline for high-dose argatroban (diamonds), low-dose argatroban (squares), or placebo (triangles). The dashed lines represent absolute changes associated with target aPTTs of 2.25× and 1.75× baseline.

*Mean±SD.
†1 additional patient treated 12.8 hours after symptom onset.
remained at or near target values throughout infusion (presented normalized as change from baseline in Figure 1). The median duration of therapy was 119 hours (range: 4 to 123) for high-dose argatroban, 106 hours (range: 2 to 121) for low-dose argatroban, and 120 hours (0.3 to 136) for placebo.

Primary Analyses: Safety

The primary outcome—symptomatic ICH—was not significantly different between patients administered high-dose argatroban (5.1%), low-dose argatroban (3.4%), or any argatroban (4.3%) versus placebo (0%; \( P = 0.18 \) ) (Table 3). No between-group differences occurred by ICH subtype (\( P = 0.50 \)). Of 5 symptomatic ICHs (Table 4), 2 were temporally unrelated to study treatment, occurring \( 7 \) days after stopping argatroban (elimination half-life, 39 to 51 minutes).\(^5\) 2 were in patients supratherapeutic (aPTT >1.75 × baseline aPTT) on high-dose argatroban, and 1 was in an elderly patient therapeutic (aPTT <1.75 × baseline aPTT) on low-dose argatroban.

No major systemic hemorrhage occurred (Table 3). Seven patients experienced asymptomatic ICH, without between-group differences (\( P = 0.61 \)). Minor systemic hemorrhage increased only with high-dose argatroban versus placebo (27.1% versus 11.1%, \( P = 0.035 \)). Survival estimates at 90 days did not differ between groups (\( P \geq 0.13 \)); 90-day mortality was 13.5% overall.

Exploration of Patient Outcomes

Neurologic assessment scores did not differ between groups at discharge/early withdrawal (range of group median scores: NIHSS, 6 to 7.5; mRS, 4; BI, 45 to 55; \( P = 0.07 \)) or 90 days (NIHSS, 1 to 2; mRS, 1 to 2; BI, 100; \( P \leq 0.40 \)). Improvements occurred in each scale over time. No between-group differences in stroke progression, as reflected by serial NIHSS scores, were detected (\( P = 0.07 \)). Success at 90 days, by each definition, did not differ between groups (Table 5). Forty-four (34%) of 129 patients with data achieved NIHSS scores of 0 to 1. Examination of data suggested differences in response by stroke subtype; however, sample sizes were small (n = 16) and there were no between-group significant differences.

Discussion

We evaluated safety and explored patient outcomes associated with argatroban anticoagulation at target aPTTs of 1.75 × and 2.25 × baseline (mean infusion doses of 1.2 and 2.7 kg/kg per minute, respectively) versus placebo in 171 patients treated within 12 hours of AIS symptom onset. The 12-hour window allowed a broad temporal evaluation of the

### Table 3. Safety Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
<th>( P ) vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic intracranial hemorrhage</td>
<td>3 (5.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>Parenchymal hemorrhage</td>
<td>1 (1.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hemorrhagic infarction</td>
<td>1 (1.7)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hemorrhagic transformation</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Major systemic hemorrhage</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Asymptomatic intracranial hemorrhage</td>
<td>1 (1.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>Minor systemic hemorrhage</td>
<td>16 (27.1)</td>
<td>0.035</td>
</tr>
<tr>
<td>Death</td>
<td>2 (3.4)</td>
<td>0.881</td>
</tr>
<tr>
<td>Within 7 days</td>
<td>2 (3.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>Within 90 days</td>
<td>7 (11.1)</td>
<td>0.68</td>
</tr>
<tr>
<td>Survival estimate (90 days)</td>
<td>0.881</td>
<td>0.13</td>
</tr>
</tbody>
</table>

\( n \) indicates not applicable/available.

### Table 4. Symptomatic Intracranial Hemorrhages

<table>
<thead>
<tr>
<th>Event</th>
<th>Study Day</th>
<th>Treatment Group</th>
<th>Maximum aPTT During Infusion, or Anticoagulation After Infusion</th>
<th>Age (y)/Gender</th>
<th>Baseline NIHSS Score</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic transformation</td>
<td>1</td>
<td>Active (high)</td>
<td>103 s (3.22 × baseline)</td>
<td>65/f</td>
<td>16</td>
<td>Died</td>
</tr>
<tr>
<td>Hemorrhagic transformation</td>
<td>1</td>
<td>Active (low)</td>
<td>49 s (1.69 × baseline)</td>
<td>83/m</td>
<td>13</td>
<td>Survived</td>
</tr>
<tr>
<td>Hemorrhagic infarction</td>
<td>4</td>
<td>Active (high)</td>
<td>68 s (2.83 × baseline)</td>
<td>80/m</td>
<td>21</td>
<td>Died</td>
</tr>
<tr>
<td>After infusion</td>
<td>13</td>
<td>Active (low)</td>
<td>Warfarin, LMWH</td>
<td>85/f</td>
<td>16</td>
<td>Died</td>
</tr>
<tr>
<td>Parenchymal hemorrhage</td>
<td>17</td>
<td>Active (high)</td>
<td>Warfarin (NR 5.2)</td>
<td>84/f</td>
<td>10</td>
<td>Lost to follow-up</td>
</tr>
</tbody>
</table>

\( m \) indicates male; \( f \), female.
safety of direct thrombin inhibition with argatroban in AIS. Placebo control was used because the only approved therapy for AIS is tissue plasminogen activator (tPA). Despite eligibility of tPA-disqualified patients, no one received study drug within 3 hours of symptoms. Patients also received aspirin. Argatroban and aspirin lack pharmacokinetic/pharmacodynamic interactions, including no interaction regarding bleeding times, an index of platelet and vascular function. Their combination use during percutaneous coronary interventions (mean argatroban dose: 23 μg/kg per minute) has low (0.9%) bleeding risk. The treatment groups were well matched with the few imbalanced characteristics, eg, age, serving as covariates in comparative regression analyses. Group mean aPTTs increased in an argatroban dose-related fashion, consistent with its predictable pharmacodynamics. A study limitation is that despite precautions to maintain blinding, it was theoretically possible for investigators to guess treatment identity, because in some cases aPTTs were recorded on hospital charts. Results indicate that intravenous argatroban administered within 12 hours of symptom onset at mean infusion doses of 1.2 and 2.7 μg/kg per minute (100-μg/kg initial bolus) for 5 days provides safe anticoagulation in AIS. Argatroban therapy versus placebo had no significant effect on the primary outcome of symptomatic ICH at 30 days or the safety outcomes of asymptomatic ICH, major systemic hemorrhage, or 90-day mortality. Minor bleeding was less common with low-dose than high-dose argatroban, perhaps related to a decreased likelihood of aPTTs > 80 seconds. These safety data are consistent with the lack of increased ICH or major bleeding in controlled studies of argatroban therapy in HIT, including patients with comorbid stroke, and in acute stroke. The data indirectly contrast with the increased serious bleeding associated with intravenous heparinoid in AIS.

In this study designed primarily to evaluate safety and not powered to evaluate efficacy, we were unable to detect a treatment effect on early stroke progression or neurologic impairment at 90 days. The positive safety profile of argatroban in AIS, taken together with clinical data supporting its benefits in stroke, particularly large-artery atherosclerotic stroke, suggest that trials to evaluate its efficacy and more precisely estimate adverse event rates are warranted. Such studies could test the hypothesis that early direct thrombin inhibition prevents extension of primary ischemic areas by reducing thrombin activity and promoting collateral flow channels. A study evaluating argatroban with tPA in acute stroke is underway.

Appendix

Individuals and Groups That Contributed to the Success of ARGIS-1

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Acknowledgments

Emcyse Pharmaceuticals, Houston, Tex supported this study. Drs LaMonte, Schultz, and Hursting have received consultancy fees from Emcyse Pharmaceuticals.

References


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Stroke. 2004;35:1677-1682; originally published online May 20, 2004; doi: 10.1161/01.STR.0000131549.20581.ba
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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