Lewis BE, Wallis DE, et al for the ARG-911 Study Investigators. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation 2001;103:1838-1843. Heparin-induced thrombocytopenia (HIT) carries a high risk of thrombosis and mortality, and requires anticoagulant therapy to reduce these risks. This 2001 study established argatroban, a direct thrombin inhibitor, as one of the anticoagulants of choice in patients with HIT. The study enrolled 304 adults with either isolated HIT or HITTS (HIT with thrombosis syndrome). Because all patients were treated with argatroban, there was no placebo arm (a placebo arm was deemed unethical, since it was already known that simply discontinuing heparin was not sufficient treatment for HIT/HITTS). Instead, they compared study patients with historical controls-- i.e., patients who developed HIT before the advent of direct thrombin inhibitors, and who were therefore managed with the standard of care at that time: heparin discontinuation +/- oral anticoagulation. The study found that argatroban therapy significantly reduced the incidence of all-cause mortality, all-cause amputation, and new thrombosis (treated as a composite endpoint) in patients with HIT compared to historical controls. Bleeding rates were found to be similar between the two groups.
Argatroban Anticoagulant Therapy in Patients With Heparin-Induced Thrombocytopenia


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Argatroban Anticoagulant Therapy in Patients With Heparin-Induced Thrombocytopenia

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Background—Heparin-induced thrombocytopenia (HIT) is an immune-mediated syndrome caused by heparin. Complications range from thrombocytopenia to thrombocytopenia with thrombosis. We report a prospective, historical-controlled study evaluating the efficacy and safety of argatroban, a direct thrombin inhibitor, as anticoagulant therapy in patients with HIT or HIT with thrombosis syndrome (HITTS).

Methods and Results—Patients with HIT (isolated thrombocytopenia, n = 160) or HITTS (n = 144) received 2 μg · kg⁻¹ · min⁻¹ IV argatroban, adjusted to maintain the activated partial thromboplastin time 1.5 to 3.0 times baseline value. Treatment was maintained for 6 days, on average. Clinical outcomes over 37 days were compared with those of 193 historical control subjects with HIT (n = 147) or HITTS (n = 46). The incidence of the primary efficacy end point, a composite of all-cause death, all-cause amputation, or new thrombosis, was reduced significantly in argatroban-treated patients versus control subjects with HIT (25.6% versus 38.8%, P = 0.014). In HITTS, the composite incidence in argatroban-treated patients was 43.8% versus 56.5% in control subjects (P = 0.13). Significant between-group differences by time-to-event analysis of the composite end point favored argatroban treatment in HIT (P = 0.010) and HITTS (P = 0.014). Argatroban therapy, relative to control subjects, also significantly reduced new thrombosis and death caused by thrombosis (P < 0.05). Argatroban-treated patients achieved therapeutic activated partial thromboplastin times generally within 4 to 5 hours of starting therapy and, compared with control subjects, had a significantly more rapid rise in platelet counts (P = 0.0001). Bleeding events were similar between groups.

Conclusions—Argatroban anticoagulation, compared with historical control subjects, improves clinical outcomes in patients who have heparin-induced thrombocytopenia, without increasing bleeding risk. (Circulation. 2001;103:1838-1843.)

Key Words: anticoagulants • inhibitors • heparin • thrombosis • platelets

Heparin-induced thrombocytopenia (HIT) is an immune-mediated syndrome characterized by thrombocytopenia, which can be isolated or associated with thrombotic events. For patients with isolated HIT, >50% are at risk for developing thrombosis. Furthermore, the mortality rate associated with HIT is ~10% to 30%. HIT is caused by the binding of antibodies (most frequently IgG) to a complex of heparin and platelet factor 4. These antibodies activate platelets through their Fc receptors, causing platelet destruction and the release of prothrombotic platelet-derived microparticles. Microparticles in turn promote thrombin generation and contribute to a hypercoagulable state. Although certain clinical situations are more likely to be associated with thrombosis, no specific laboratory or clinical characteristic can predict which patient will have isolated thrombocytopenia or have thrombocytopenia with thrombotic complications. Thrombotic events are most frequently venous, but arterial thrombosis leading to myocardial infarction and ischemic limb damage requiring amputation also occur.
The discontinuation of heparin is recommended for managing HIT; however, treatment strategies such as alternate anticoagulants should be considered. Approximately 40% to 50% of HIT patients will have a thrombotic event when heparin is discontinued. Additionally, many patients require ongoing anticoagulation for underlying medical conditions. Alternative agents that have been used in this setting include warfarin, ancrod, low-molecular-weight heparin, danaparoid, and recombinant hirudin (lepirudin). Thrombotic event rates, however, have generally remained high, and there are disadvantages associated with these agents. For example, warfarin has been associated with worsening of the thrombotic event in patients with HIT. The defibrinogenating agent ancrod does not inhibit thrombin, which is a significant problem for patients with HIT. Low-molecular-weight heparin and, to a lesser extent, danaparoid, cross-react with HIT antibodies.

Direct thrombin inhibition may be beneficial in managing HIT. In 1 of 2 trials, lepirudin significantly improved clinical outcomes in HIT patients, relative to historical control subjects. Lepirudin is renally cleared, and ≈50% of lepirudin-treated patients develop drug-specific antibodies that can alter its anticoagulant effects, hence complicating monitoring and dosing, particularly in patients with renal failure or insufficiency. Argatroban, also a direct thrombin inhibitor, is a small, synthetic molecule that binds reversibly and specifically to the catalytic domain of thrombin. Argatroban is heparinically metabolized but not renally cleared, and drug-specific antibodies have not been known to develop.

We report a prospective study evaluating the efficacy and safety of argatroban as an anticoagulant in patients with HIT or HIT with thrombosis syndrome (HITTS). When this study was initiated, no approved alternative agent was available for use as an active comparator, and a randomized, placebo-controlled design was deemed unethical. Therefore, historical control subjects were studied for comparison.

Methods

Study Design

The institutional review board at each participating center approved this multicenter, nonrandomized, open-label, historical-controlled trial before its initiation, and patient informed consent was obtained. Men and nonpregnant, nonbreastfeeding women 18 to 80 years old were eligible. Patients were assigned at enrollment to either the HIT study arm (for those with isolated HIT) or HITTS study arm (for those with HIT complicated by thrombosis that occurred after heparin initiation). Eligible patients had thrombocytopenia, defined as a platelet count <100×10^9/L or a 50% reduction in count after heparin therapy with no explanation besides HIT. Patients who had documented history of positive HIT antibody (ie, latent disease) and who required anticoagulation were eligible for the HIT arm, in the absence of thrombocytopenia or heparin challenge. Any patient with an unexplained activated partial thromboplastin time (aPTT) >2 times control at baseline, documented coagulation disorder or bleeding diathesis unrelated to HITTS, a lumbar puncture within the past 7 days, or a history of previous aneurysm, hemorrhagic stroke, or recent (within 6 months) thrombotic stroke unrelated to HITTS was excluded. Patients underwent a 2-tier medical review with adjudication, with differences in attribution adjudicated by a panel of physicians not related to the trial. Study baseline was the date argatroban therapy was initiated.

Potential historical control cases were identified by means of prospectively agreed on, documented approaches, which included a review of laboratory logs of patients who were tested for HIT or were thrombocytopenic. Potential control subjects were seen typically within 4 years before study initiation at participating centers and met these same inclusion/exclusion criteria per chart review by the investigator. Control subjects were treated according to the local standard of practice at the time of HIT diagnosis, with typical treatments being heparin discontinuation and/or oral anticoagulation. To minimize site-specific, nongeneralizable outcomes, a center could enroll up to 3 control subjects, in chronological order of their identification, per prospective patient enrolled. Case report forms were completed for 213 potential control patients. Case information underwent a 2-tier medical review with adjudication as described above. Patients found eligible made up the control group (n = 193). Study baseline for control subjects was the data that heparin was discontinued after the platelet count met inclusion criteria or that the count met inclusion criteria after heparin initiation.

Treatment and Assessments

Heparin was discontinued for prospective patients, and continuous intravenous argatroban (Texas Biotechnology Corporation; SmithKline Beecham Pharmaceuticals) was initiated at 2 μg·kg⁻¹·min⁻¹. The aPTT was determined 2 hours later at each site, and dosage was adjusted (up to 10 μg·kg⁻¹·min⁻¹, maximum) until the aPTT was 1.5 to 3.0 times the baseline aPTT value (not to exceed 100 seconds). The aPTT was measured daily and 2 hours after each dosage adjustment. Patients received argatroban until the underlying condition was clinically resolved, appropriate anticoagulation was provided with other agents, or treatment was continued for 14 days.

Patients were followed from baseline, during treatment, and for 30 days after therapy cessation. Control subjects were followed for 37 days from baseline. Death (all causes), death caused by thrombosis (per investigator’s assessment), amputation (all causes), new thrombosis, and bleeding events were recorded. Major bleeding was defined as overt and associated with a hemoglobin decrease ≥2 g/dL that led to a transfusion of ≥2 U or that was intracranial, retroperitoneal, or into a prosthetic joint. Other bleeding was considered minor. The primary efficacy assessment was a composite end point of all-cause death, all-cause amputation, or new thrombosis within 37 days of baseline. Secondary efficacy assessments included the individual components of the composite end point, death caused by thrombosis, any new thrombosis, achievement of adequate anticoagulation (ie, aPTT ≥1.5 times baseline aPTT value), and resolution of thrombocytopenia. Thrombocytopenia was resolved during treatment if it resolved within 4 days after argetroban infusion (or within 7 days of baseline for control subjects) a baseline platelet count of <100×10^9/L increased to ≥100×10^9/L or if a baseline platelet count of ≥100×10^9/L remained at the same level or increased during treatment. Thrombocytopenia was resolved within 3 days of baseline if the platelet count was >100×10^9/L or >1.5 times baseline value.

Data Analyses and Statistics

Using literature estimates of composite end point rates for HIT/HITTS (30% to 50%), we estimated that 150 argatroban-treated patients per arm, at least 60 HIT control subjects, and 50 HITTS control subjects would allow detection (β = 0.10, α = 0.01) of a significant treatment effect (absolute difference in composite end point rate of ≥20%). Analyzes were conducted separately for the study arms. Hypothesis testing was 2-sided, with significance at a level of P ≤ 0.05. No adjustments were made for multiple comparisons. Demographic and baseline characteristics were compared between groups by means of the Student’s t test (age, weight) or Fisher’s exact test (sex, percent test positive by heparin-induced platelet aggregation test?) or serotonin release assay27). Between-group analysis of the composite end point was performed by categorical and time-to-event (Kaplan-Meier lifetime tables) methods, with statistical significance assessed by means of the χ² test and log-rank test, respectively. For time-to-event analyses, patients were censored on the last day of follow-up or on death (all causes). We looked at endpoint outcomes after 37 days, whichever came first. Hazard ratios and 95% CIs were
estimated by proportional hazards regression analysis. Between-group comparisons for the composite end point’s individual components (distributed by severity), death caused by thrombosis, and any new thrombosis were performed by means of Fisher’s exact test. ANCOVA was performed on the change in platelet count by study day 3, with baseline platelet count taken as covariate.

Results
This trial enrolled 304 argatroban-treated patients (n=160, HIT arm; n=144, HITTS arm) for comparison with 193 historical control subjects (n=147, HIT arm; n=46, HITTS arm). The HIT study arm included 31 argatroban-treated patients and 8 historical control subjects without thrombocytopenia yet with a history of a positive HIT antibody test and requiring anticoagulation. Table 1 summarizes patient demographic and baseline characteristics. Between-group differences were detected in both arms for age and in the HIT arm for sex and test positivity. Median baseline platelet counts were lower among argatroban-treated patients than control subjects.

The mean (±SE) argatroban dose in the HIT and HITTS arm, respectively, was 2.0±0.1 µg·kg⁻¹·min⁻¹ and 1.9±0.1 µg·kg⁻¹·min⁻¹, and the duration of therapy was 5.3±0.3 days and 5.9±0.2 days, respectively. Of 304 argatroban-treated patients, 252 (83%) completed the protocol-specified treatment period; 30 (10%) prematurely discontinued infusion because of surgery (6), patient request (3), or other reasons (21; eg, increased aPTT, positive blood culture, decision to withdraw life support); and 22 (7%) were withdrawn because of adverse events. Events leading to withdrawal of >1 patient were coagulopathy, anemia, and gastrointestinal hemorrhage (2 patients each) and unspecified hemorrhage (3 patients).

Primary Efficacy End Point
The incidence of the composite end point was reduced significantly in argatroban-treated patients versus control subjects with HIT (25.6% versus 38.8%, P=0.014). In HITTS, the composite end point occurred in 43.8% of argatroban-treated patients compared with 56.5% of control subjects (P=0.014; hazard ratio = 0.57; 95% CI, 0.36 to 0.90).

Table 1. Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>HIT Arm</th>
<th>HITTS Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Argatroban</td>
</tr>
<tr>
<td></td>
<td>n=147</td>
<td>n=160</td>
</tr>
<tr>
<td>Age, y (mean±SD)</td>
<td>66.1±12.3</td>
<td>61.3±13.5*</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83 (56)</td>
<td>68 (43)*</td>
</tr>
<tr>
<td>Female</td>
<td>64 (44)</td>
<td>92 (57)*</td>
</tr>
<tr>
<td>Weight, kg (mean±SD)</td>
<td>80.0±22.8</td>
<td>78.9±18.6</td>
</tr>
<tr>
<td>Test positive,†n (%)</td>
<td>119 (81)</td>
<td>80 (50)*</td>
</tr>
<tr>
<td>Baseline platelets,×10⁹/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>111</td>
<td>82</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>79–159</td>
<td>51–145</td>
</tr>
<tr>
<td>Circulatory disease</td>
<td>126 (66)</td>
<td>160 (100)</td>
</tr>
</tbody>
</table>

*P<0.05 vs control group.
†Positive heparin-induced platelet aggregation test or serotonin release assay. Results for remainder of patients was negative or not determined.

Figure 1. Time to first event for composite end point: HIT study arm. Data are presented for argatroban-treated patients (solid line; n=160, censored=119) and historical control subjects (dashed line; n=147, censored=90) (P=0.010; hazard ratio = 0.60; 95% CI, 0.40 to 0.89), with tick marks indicating days that patients were censored. Number of patients at risk is presented for days 7, 14, 21, 28, and 37.

Figure 2. Time to first event for composite end point: HITTS study arm. Data are presented as in Figure 1 for argatroban-treated patients (solid line; n=144, censored=81) and historical control subjects (dashed line; n=46, censored=20) (P=0.014; hazard ratio = 0.57; 95% CI, 0.36 to 0.90).
argatroban treatment in both the HIT arm ($P=0.010$, hazard ratio = 0.60, 95% CI = 0.40 to 0.89; Figure 1) and HITTS arm ($P=0.014$, hazard ratio = 0.57, 95% CI = 0.36 to 0.90; Figure 2). Treatment effect remained a significant predictor of the time-to-first event also after adjusting for patient age, test positivity, race, and baseline medical conditions (HIT, $P = 0.001$; HITTS, $P = 0.027$).

### Secondary Efficacy End Points

Table 2 summarizes the between-group comparative analyses for the incidence of death caused by thrombosis, new thrombosis, and each individual component of the composite end point. In both arms, argatroban-treated patients compared with control subjects had significantly reduced death caused by thrombosis ($P=0.005$). There were no between-group differences in all-cause mortality. The incidence of amputation (as the most severe outcome) was similar between groups. Argatroban therapy significantly reduced the percentage of patients with new thrombosis in both study arms ($P=0.044$). New thrombotic events occurring in argatroban-treated patients were primarily (86%) in the venous circulation.

Thrombocytopenia was resolved in ≥69% of argatroban-treated patients (compared with ≤50% of control subjects) during the treatment interval and in ≥53% of argatroban-treated patients by day 3 (Table 3). For the HIT and HITTS arms, mean (±SE) changes in platelet count by day 3 were +54 (±7) $\times 10^9$/L and +52 (±7) $\times 10^9$/L, respectively, for argatroban-treated patients, compared with −33 (±10) $\times 10^9$/L and −21 (±19) $\times 10^9$/L, respectively, for control subjects ($P=0.0001$, each arm). By conclusion of treatment, median platelet counts for argatroban-treated patients were 185.5$\times 10^9$/L in the HIT arm and 198$\times 10^9$/L in the HITTS arm.

Adequate anticoagulation with argatroban was achieved in ≥83% of patients during the study and generally within 4 to 5 hours of initiation of infusion (Table 4). Median aPTTs increased from 29.9 seconds at baseline in the HIT and HITTS arms to 60.4 (interquartile range, 51.0 to 71.8) seconds and 67.5 (53.9 to 83.4) seconds, respectively, within 12 hours of argatroban initiation. During infusion, aPTTs remained steady, with median daily values of 52.2 to 62.6 seconds in the HIT arm and 52.4 to 68.0 seconds in the HITTS arm.

### Safety

Major bleeding rates were not different between the argatroban-treated patients and control subjects in either study arm (Table 5). One argatroban-treated patient had an intracranial hemorrhage, which the investigator deemed unrelated to study medication, 4 days after discontinuing argatroban and after warfarin and urokinase therapy. Another patient developed disseminated intravascular coagulation while receiving argatroban, warfarin, citrate, aspirin, and streptokinase and died of multiosystem hemorrhage. Two fatal bleeding events, including 1 intracranial hemorrhage, oc-

### Table 2. Categorical Efficacy Analyses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIT Arm</th>
<th>Argatroban (n=160)</th>
<th>Control (n=147)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite end point*</td>
<td>57 (38.8)</td>
<td>41 (25.6)</td>
<td>$0.014$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Odds ratio = 0.54 (95% CI, 0.33–0.88)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Components by severity†</td>
<td>32 (21.8)</td>
<td>27 (16.9)</td>
<td>$0.311$</td>
<td></td>
</tr>
<tr>
<td>Death (all causes)</td>
<td>3 (2.0)</td>
<td>3 (1.9)</td>
<td>$1.000$</td>
<td></td>
</tr>
<tr>
<td>Amputation (all causes)</td>
<td>22 (15.0)</td>
<td>11 (6.9)</td>
<td>$0.027$</td>
<td></td>
</tr>
<tr>
<td>New thrombosis</td>
<td>7 (4.8)</td>
<td>0 (0.0)</td>
<td>$0.005$</td>
<td></td>
</tr>
<tr>
<td>Death caused by thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any new thrombosis‡</td>
<td>33 (22.4)</td>
<td>13 (8.1)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%).  
*All-cause death, all-cause amputation, or new thrombosis within 37-day study period.  
†Severity ranking: all-cause death > all-cause amputation > new thrombosis; patients with multiple outcomes counted once.  
‡Patient counted only once if multiple events occurred.

### Table 3. Resolution of Thrombocytopenia*

<table>
<thead>
<tr>
<th>HIT Arm</th>
<th>Argatroban (n=160)</th>
<th>Control (n=147)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>During treatment†</td>
<td>57/139 (41)</td>
<td>104/129 (81)</td>
<td></td>
</tr>
<tr>
<td>Within 3 d of baseline‡</td>
<td>. . .</td>
<td>56/105 (53)</td>
<td></td>
</tr>
</tbody>
</table>

Values are no. achieved (%).  
*See Methods for definition.  
†Patients in HIT arm with latent disease excluded; patients with missing data considered failures.  
‡Analysis performed only on argatroban group; patients with missing data excluded. 95% CIs: HIT, 44% to 64%; HITTS, 48% to 68%.
HIT antibodies, 25 a disadvantage of low-molecular-weight heparin does not resemble heparin, it does not cross-react with HIT, 3.9 (2.9) hours. Assessment for those achieving adequate anticoagulation: HIT, 4.6 (2.9) hours; HITTS, 73% to 87%. Mean (median) time to first event, a composite of death, amputation, or new thrombosis, was selected to reflect major morbidity and mortality associated with the disease. Also, the time required for resolution of thrombocytopenia, an important marker of ongoing HIT activity, was monitored.

Although not ideal, a historical-control study design may be necessary when it is important to compare treatments, but a comparative treatment is not available. Furthermore, the participants in our trial believed that it would be unethical to use a placebo or withhold a treatment that has been shown in preliminary studies to be effective. For example, >50% of patients with isolated HIT who are treated simply by stopping heparin will have thrombosis within 30 days.1 Hence, treatment by observation or placebo was considered unacceptable, and comparison with a historical control group was used.

There are known scientific limitations with a historical comparator, including different methods of event ascertainment for historical control subjects and treated patients. Among control subjects, events may be underreported because data are initially collected for different purposes or possibly overreported because cases may have been specifically recognized as a result of their events. We attempted to minimize such bias by identifying potential control subjects by approaches such as reviewing laboratory logs of patients who were tested for HIT and were thrombocytopenic and by having control subjects (and treated patients) independently adjudicated. We also tried to limit possible event underreporting in the unblinded treatment group by having duplex Doppler examinations and ventilation/perfusion scans performed at baseline and end of the study.

Another possible concern of historical comparators is referral bias, wherein prospective patients may have more advanced illness than control subjects because of the potential...
for medical “watchful waiting” when an investigational agent is available. However, this bias would favor control. To try to minimize this problem, we applied the same inclusion and exclusion criteria to both groups. Changing management practices may also be an issue with historical control subjects. Herein, control subjects typically were seen within 4 years before study initiation at participating sites, and we aimed to minimize variability in practice by limiting each site to 3 control subjects per treated patient. Our overall impression is that these biases, if operational, would tend to mask, not exaggerate, the true differences between the groups.

Our study demonstrated that argatroban treatment of patients with HIT produced significant benefits in clinical outcomes and disease progression compared with historical control subjects. Specifically, argatroban therapy significantly reduced the risk of a composite of death, amputation, or new thrombosis; the risk of death caused by thrombosis; and the risk of new thrombosis. Additionally, argatroban-treated patients had a more rapid recovery of the platelet count. These benefits were realized without increased bleeding risk, compared with control subjects. Therefore, in patients with heparin-induced thrombocytopenia, argatroban is effective in lowering mortality rates from thrombosis and preventing new thrombotic events with an acceptable risk-benefit ratio. Hence, argatroban offers a therapeutic alternative for these patients in whom current options are limited.

Appendix

Principal Investigator was B. Lewis.

Investigators


Hemostasis Core Laboratory

J. Fareed and J. Walenga.

Independent Medical Reviewers


Acknowledgments

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References


