Effects of Argatroban Therapy, Demographic Variables, and Platelet Count on Thrombotic Risks in Heparin-Induced Thrombocytopenia*

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Study objectives: We investigated the effects of the direct thrombin inhibitor argatroban, patient demographics, and the platelet count on thrombotic risks in heparin-induced thrombocytopenia (HIT), a serious thrombotic condition, to determine if argatroban provides effective antithrombotic therapy in patients with HIT without increasing bleeding.

Design: We retrospectively analyzed thrombotic outcomes in 882 HIT patients (697 patients receiving mean argatroban doses of 1.7 to 2.0 μg/kg/min for 5 to 7 days, plus 185 historical control subjects) from previously reported prospective studies. Time-to-event analyses of our primary end point—a thrombotic composite of death due to thrombosis, amputation secondary to HIT-associated thrombosis, or new thrombosis within 37 days—and the individual components were conducted, with hazard ratios estimated for treatment with and without adjustments for patient age, gender, race, weight, and baseline platelet count.

Measurements and results: Argatroban, vs control, significantly reduced the thrombotic composite risk (HIT: hazard ratio, 0.33; 95% confidence interval [CI], 0.20 to 0.54, p < 0.001; HIT with thrombosis: hazard ratio, 0.39; 95% CI, 0.25 to 0.62, p < 0.001), regardless of covariate adjustments. More argatroban-treated patients than control subjects remained thrombotic event free during follow-up, regardless of whether baseline thrombosis was present (72% vs 50%). Argatroban significantly reduced new thrombosis (p < 0.001) and death due to thrombosis (p ≤ 0.001). Major bleeding was similar between groups (6 to 7%, p = 0.74). Thrombotic risks were 2 times greater in nonwhite than in white patients, 1.7 times greater in female than male patients with HIT and thrombosis, and increased with decreasing weight or platelet count.

Conclusions: Argatroban, vs control, provides effective antithrombotic therapy in patients with HIT, without increasing bleeding. Patients at higher risk for HIT-associated thrombosis include women, nonwhites, and individuals with current HIT-associated thrombosis, lower body weight, or more severe thrombocytopenia.

Key words: argatroban; heparin; heparin-induced thrombocytopenia; platelets; thrombocytopenia; thrombosis

Abbreviations: aPTT = activated partial thromboplastin time; CI = confidence interval; HIT = heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a serious, immune-mediated thrombotic disorder occurring in approximately 1 to 5% of patients receiving heparin therapy for ≥1 week. In HIT, antibodies to heparin-platelet factor 4 complexes cause platelet activation, excessive thrombin generation, thrombocytopenia, and often fatal or nonfatal thrombosis. Mortality in HIT patients with thrombosis is approximately 17 to 30%. HIT should be suspected whenever the platelet count falls at least 50% and/or thrombosis occurs between day 4 and day 14 following initiation of heparin (or sooner if the patient was exposed to heparin in the past 3 months). According to consensus treatment guidelines, when HIT with or without thrombosis is strongly suspected, all heparins should be avoided and alternative parenteral anticoagulation should be initiated.
Two direct thrombin inhibitors—argatroban and lepirudin—are approved in the United States for use as alternative parenteral anticoagulants in patients with HIT. In prospective, historically controlled studies, argatroban and lepirudin have each been shown to improve general outcomes in patients with HIT, reducing a primary composite end point of all-cause death, all-cause amputation, or new thrombosis. However, because “all-cause” composite end points can be confounded by numerous clinical factors, particularly in critically ill patients with multiple medical conditions, the antithrombotic effect of direct thrombin inhibition in HIT remains to be specifically estimated. Risk factors identified to date for progression to thrombosis in HIT include comorbid malignancy for panvascular thrombosis and female gender for ischemic stroke. Also, the severity of thrombocytopenia has been shown to be a significant independent predictor of the all-cause composite end point or new thrombosis in the studies of direct thrombin inhibition in HIT. Further characterization of risk factors of HIT-associated thrombotic events would be useful for facilitating HIT risk assessment, particularly in patients presenting with thrombotic symptoms requiring urgent care.

For editorial comment see page 1396

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Materials and Methods

This retrospective analysis of thrombotic outcomes in patients with HIT included 582 patients from prospective, multicenter, historical controlled studies: the Argatroban-911 study and the Argatroban-915 study plus its extension, the Argatroban-915X study. The studies evaluated the safety and efficacy of argatroban therapy in HIT and were conducted between 1995 and 1998. For purposes of this analysis, the Argatroban-915 study and its extension the Argatroban-915X study are considered as separate studies. The Institutional Review Board at each center approved each study before its initiation. Subjects gave informed consent.

Study Design

The studies have been previously described (Table 1). In brief, adult patients with clinically diagnosed HIT were discontinued from heparin and administered IV argatroban, 2 μg/kg/min, adjusted to achieve an activated partial thromboplastin time (aPTT) of 1.5 to 3 times the baseline value. When the studies were conducted, no approved comparator existed and placebo administration was considered unethical. Thus, in each study comparisons were made with a historical control cohort from the Argatroban-911 study. The control patients met the same inclusion and exclusion criteria by chart review as prospectively treated patients; most presented in the 4 years before study initiation. The typical treatment for control patients was heparin discontinuation and/or dextran, antiplatelet, or warfarin therapy; they did not receive antithrombin therapy. All patients were stratified at baseline according to the absence or presence of thrombosis that had occurred after initiation of heparin (ie, HIT or HIT with thrombosis, respectively). Although not required for study enrollment, a positive laboratory result confirmed HIT in most patients. Study baseline for the argatroban-treated patients was the date that therapy was initiated; for the control patients, the date was when heparin was discontinued after the platelet count met inclusion criteria or the date that the platelet count reached threshold after heparin initiation.

Setting

All patients were hospitalized, often in acute care settings. Some patients initially presented in the emergency department.

Selection of Participants

The population for our retrospective analysis included all patients with clinically diagnosed HIT from the prospective studies (ie, 273 patients from the Argatroban-911 study, 247 patients from the Argatroban-915 study, and 177 patients from Argatroban-915X study). All patients were hospitalized, often in ICUs.

Outcome Measures

Patients were followed up prospectively from baseline, during treatment, and for 30 days after therapy cessation. Control subjects were followed up for 37 days from baseline. Outcomes recorded included death, including death due to thrombosis or to another cause; amputation, including amputation secondary to HIT-associated thrombosis or to another cause; new thrombosis;
Argatroban dosing and monitoring

Exclusion criteria

- Clinically diagnosed HIT, defined as a platelet count $< 100 \times 10^9/L$, or 50% reduction in count, following heparin therapy with no apparent explanation other than HIT

Inclusion criteria

- Terminal illness with life expectancy $< 2$ wk (Argatroban-915 and extension studies)

Argatroban dosing and monitoring

- Initial infusion rate of 2ug/kg/min*
- Dose was adjusted (up to 10ug/kg/min) until the aPTT was 1.5 to 3 times the baseline value (not to exceed 100 s)
- Argatroban was continued until underlying condition resolved, appropriate anticoagulation was provided with other agents, or for 14 d
- aPTT was determined 2 h after initiation of infusion, 2 h after dose adjustment, and daily

Outcomes (37-d follow-up)

- Death from all causes; death due to thrombosis
- Amputation from all causes; amputation secondary to HIT-associated thrombosis
- New thrombosis
- Major bleeding

*A lower starting dose was allowed if needed owing to the patient’s medical condition (the presence of hepatic impairment).

and major bleeding. The attribution of the cause of death or amputation was determined by the physician investigator. Death from a cause not related to thrombosis or HIT, such as aspiration pneumonia, was attributed to another cause. Amputation related to a condition such as infection that was not the result of thrombosis secondary to HIT was attributed to another cause. New thrombosis was clinically diagnosed and/or objectively documented using noninvasive techniques (e.g., ventilation/perfusion scanning or ultrasound examinations). Major bleeding was defined as overt hemorrhage associated with a hemoglobin decrease $\geq 2$g/dL that led to a transfusion of $\geq 2$U, or hemorrhage was intracranial, retroperitoneal, or into a prosthetic joint.

For this analysis, the primary end point was a composite of death due to thrombosis, amputation secondary to HIT-associated thrombosis, or new thrombosis within 37 days of baseline (referred to as the “thrombotic composite”). Secondary efficacy end points included the individual components of the thrombotic composite.

Data Analysis

All statistical analyses were performed using statistical software (SAS version 8.2, SAS Institute; Cary, NC). Hypothesis testing was two sided and conducted at the 0.05 level of significance. Analyses were performed on patients stratified according to their HIT status at baseline (i.e., with or without thrombosis). Demographic characteristics and baseline platelet count were compared between treatment and control groups by means of the Wilcoxon rank-sum test (age, weight, and platelet count) or Fisher exact test (gender and race).

The primary analysis was the time-to-event analysis of the thrombotic composite for the studies individually and combined. This analysis was performed using the product-limit method, with between-group statistical significance assessed using the log-rank test. A patient was considered censored on day 37 or the last follow-up day, whichever came first, unless the patient had the end point. A test for homogeneity of Cox proportional hazard parameter estimates was used to evaluate for consistency of treatment effect across studies. Consistency was demonstrated, and additional analyses were conducted on data combined from the individual studies. Cox proportional hazards models were used to estimate the hazard ratio, with 95% confidence interval (CI). The models included treatment effect with (designated model B) and without (designated model A) adjusting for patient age, gender, race, weight, and baseline platelet count. The Cox proportional hazards analyses were repeated for each component of the thrombotic composite end point. For the treatment and control groups separately, time-to-event analyses were also conducted for new thrombosis by HIT presentation. The incidence of major bleeding was compared between treatment and control groups using Fisher exact test.

Results

Analysis Population

This analysis evaluated the thrombotic-associated outcomes of 882 patients, including 697 patients who were prospectively treated with argatroban and 185 control patients who were not treated with antithrombin therapy. Approximately one half of the patients in this study had HIT ($n = 460, 52\%$), and the rest of the patients had HIT with thrombosis ($n = 422, 48\%$) at the initial diagnosis. With the exception of gender and race distributions in HIT patients without thrombosis, the treatment and control groups were similar with respect to demographic characteristics and baseline platelet counts, which generally reflected moderately severe thrombocytopenia (Table 2).
Primary Thrombotic Composite End Point

Time-to-event analyses of the thrombotic composite end point of death due to thrombosis, amputation secondary to HIT-associated thrombosis, or new thrombosis within 37 days of baseline demonstrated consistent and favorable antithrombotic effects of argatroban, compared with control, in patients with HIT (Fig 1, upper panel) or HIT with thrombosis (Fig 1, lower panel). Separation between the time-to-event curves of the argatroban-treated patients compared with control subjects was observed within days in each presentation of HIT, with a particularly pronounced early separation occurring in patients with HIT with thrombosis (Fig 1, lower panel). Cox proportional hazards model parameter estimates for the treatment effect were similar across the Argatroban-911, Argatroban-915, and Argatroban-915X studies for HIT (p = 0.74) or HIT with thrombosis (p = 0.71), and hence the combined data of argatroban-treated patients from these three studies was used in all subsequent HIT and HIT with thrombosis analyses.

For the combined data, argatroban therapy, compared with control, significantly reduced the risk for the thrombotic composite in both HIT presentations (model A) [HIT: hazard ratio, 0.33; 95% CI, 0.20 to 0.54, p < 0.001; HIT with thrombosis: hazard ratio, 0.39; 95% CI, 0.25 to 0.62, p < 0.001; Table 3]. The antithrombotic benefits of argatroban therapy remained highly significant after adjusting for patient demographics and baseline platelet count (model B) [HIT: adjusted hazard ratio, 0.27; 95% CI, 0.15 to 0.49, p < 0.001; HIT with thrombosis: adjusted hazard ratio, 0.42; 95% CI, 0.23 to 0.77, p = 0.005; Table 3].

The percentage of argatroban-treated HIT patients who remained free of the thrombotic composite was 91% for individuals presenting with isolated thrombocytopenia (compared with 73% in control subjects, p < 0.001) and 72% for individuals presenting with HIT-associated thrombosis (compared with 50% in control subjects, p < 0.001; Table 4).

Components of the Thrombotic Composite

Irrespective of the HIT presentation, with or without HIT-associated thrombosis, argatroban therapy significantly reduced the risk of new thrombosis (HIT: hazard ratio, 0.29; 95% CI, 0.17 to 0.50; p < 0.001; HIT with thrombosis: hazard ratio, 0.32; 95% CI, 0.18 to 0.55; p < 0.001; Fig 2) and death due to thrombosis (HIT: hazard ratio, 0.072; 95% CI, 0.009 to 0.60, p = 0.015; HIT with thrombosis: hazard ratio, 0.13; 95% CI, 0.05 to 0.40, p < 0.001), compared with control therapy (Table 3). These treatment benefits remained significant after adjusting for patient demographics and baseline platelet count. There were no between-group differences in the risk of amputation secondary to HIT-associated thrombosis (Table 3).

A total of 48 argatroban-treated patients (16 patients in the Argatroban-911 study, 18 patients in the Argatroban-915 study, and 14 patients in the Argatroban-915X study) and 8 historical control subjects underwent amputation secondary to HIT-associated thrombosis. By comparison, 60 argatroban-treated patients (20 patients in the Argatroban-911 study, 24 patients in the Argatroban-915 study, and 16 patients in the Argatroban-915X study) and 9 historical control subjects from the previous studies\(^5,6\) underwent amputation from any cause. Hence, amputation in 12 argatroban-treated patients and 1 control subject was attributed to a cause other than HIT-associated thrombosis.

Consistent with these findings, significantly more

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**Table 2—Baseline Characteristics of the Analysis Population (n = 882)**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>HIT (n = 460)</th>
<th>p Value</th>
<th>HIT With Thrombosis (n = 422)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Argatroban (n = 321)</td>
<td>Control (n = 139)</td>
<td></td>
<td>Argatroban (n = 376)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>63 ± 14</td>
<td>65 ± 12</td>
<td>0.12</td>
<td>63 ± 14</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>0.042</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>151 (47)</td>
<td>80 (58)</td>
<td></td>
<td>188 (50)</td>
</tr>
<tr>
<td>Female</td>
<td>170 (53)</td>
<td>59 (42)</td>
<td></td>
<td>188 (50)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>278 (87)</td>
<td>116 (83)</td>
<td>0.11</td>
<td>331 (88)</td>
</tr>
<tr>
<td>Black</td>
<td>26 (8)</td>
<td>8 (6)</td>
<td></td>
<td>28 (7)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 (2)</td>
<td>3 (2)</td>
<td></td>
<td>7 (2)</td>
</tr>
<tr>
<td>Asian</td>
<td>6 (2)</td>
<td>0 (0)</td>
<td></td>
<td>6 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (1)</td>
<td>12 (9)</td>
<td></td>
<td>4 (1)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76 ± 19</td>
<td>80 ± 22</td>
<td>0.17</td>
<td>84 ± 21</td>
</tr>
<tr>
<td>Platelet count, (\times 10^9/L)</td>
<td>82 ± 59</td>
<td>82 ± 41</td>
<td></td>
<td>81 ± 81</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No. (%).
argatroban-treated patients, vs control patients, remained free of new thrombosis (HIT: 93% vs 76%, p < 0.001; HIT with thrombosis: 83% vs 62%, p < 0.001) and of death due to thrombosis (HIT: 99.7% vs 95%, p = 0.0013; HIT with thrombosis: 98% vs 87%, p < 0.001) during the study period (Table 4). Although argatroban therapy did not affect the rate of amputation in both the HIT group and the HIT with thrombosis group, more patients in the HIT with thrombosis group (13%) underwent amputation secondary to HIT-associated thrombosis than patients in the HIT group (2 to 3%; Table 4). Consistently across outcomes and patient groups (ie, treatment and control), untoward events occurred less often in HIT patients presenting with isolated thrombocytopenia than with HIT-associated thrombosis (Table 4).

While receiving argatroban therapy, 74 patients had the thrombotic composite, 48 patients had new thrombosis, 28 patients underwent amputation secondary to HIT-associated thrombosis, and 3 patients died due to thrombosis. While not receiving argatro-
ban therapy, but within the 37-day study window, 49 patients had the thrombotic composite, 30 patients had new thrombosis, 20 patients underwent amputation secondary to HIT-associated thrombosis, and 5 patients died due to thrombosis.

Consideration of Risk Factors for Thrombosis-Related Outcomes in HIT

Thrombotic Composite: Table 3 presents Cox proportional hazard regression modeling with treatment and patient age, gender, race, weight, and baseline platelet count as covariates. White patients had significantly less risk than nonwhite patients for the thrombotic composite, irrespective of the HIT presentation (HIT: adjusted hazard ratio, 0.43; 95% CI, 0.21 to 0.86, p = 0.017; HIT with thrombosis: adjusted hazard ratio, 0.49; 95% CI, 0.27 to 0.87, p = 0.014). Men had significantly less risk than women patients for the thrombotic composite in HIT patients with thrombosis (adjusted hazard ratio, 0.60; 95% CI, 0.38 to 0.98, p = 0.034). The relative risk for the thrombotic composite end point

Table 3—Cox Proportional Hazard Analysis of the Thrombotic Composite End Point and Its Components*

<table>
<thead>
<tr>
<th>Covariates</th>
<th>HIT</th>
<th></th>
<th>HIT With Thrombosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>p Value</td>
<td>Hazard Ratio (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Thrombotic composite end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model A: argatroban</td>
<td>0.33 (0.20–0.54)</td>
<td>&lt; 0.001</td>
<td>0.39 (0.25–0.62)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Model B: argatroban</td>
<td>0.27 (0.15–0.49)</td>
<td>&lt; 0.001</td>
<td>0.42 (0.23–0.77)</td>
<td>0.005</td>
</tr>
<tr>
<td>Age, yr</td>
<td>0.99 (0.97–1.01)</td>
<td>0.32</td>
<td>1.00 (0.98–1.02)</td>
<td>0.98</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.17 (0.61–2.23)</td>
<td>0.64</td>
<td>0.60 (0.38–0.96)</td>
<td>0.034</td>
</tr>
<tr>
<td>White race</td>
<td>0.43 (0.21–0.86)</td>
<td>0.017</td>
<td>0.49 (0.27–0.87)</td>
<td>0.014</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>0.98 (0.96–0.998)</td>
<td>0.029</td>
<td>1.00 (0.99–1.01)</td>
<td>0.64</td>
</tr>
<tr>
<td>Platelet count, × 10^9/L</td>
<td>0.99 (0.99–1.00)</td>
<td>0.056</td>
<td>1.00 (0.99–1.00)</td>
<td>0.13</td>
</tr>
<tr>
<td>Death due to thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model A: argatroban</td>
<td>0.072 (0.009–0.60)</td>
<td>0.015</td>
<td>0.13 (0.045–0.40)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Model B: argatroban</td>
<td>0.083 (0.009–0.77)</td>
<td>0.028</td>
<td>0.19 (0.05–0.69)</td>
<td>0.012</td>
</tr>
<tr>
<td>Age, yr</td>
<td>1.03 (0.95–1.12)</td>
<td>0.43</td>
<td>1.00 (0.95–1.05)</td>
<td>0.98</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.51 (0.07–3.57)</td>
<td>0.50</td>
<td>1.02 (0.26–3.98)</td>
<td>0.98</td>
</tr>
<tr>
<td>White race</td>
<td>0.92 (0.09–9.04)</td>
<td>0.94</td>
<td>0.35 (0.09–1.40)</td>
<td>0.14</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>0.99 (0.94–1.04)</td>
<td>0.63</td>
<td>1.01 (0.98–1.04)</td>
<td>0.52</td>
</tr>
<tr>
<td>Platelet count, × 10^9/L</td>
<td>1.01 (0.99–1.02)</td>
<td>0.30</td>
<td>1.00 (0.98–1.01)</td>
<td>0.55</td>
</tr>
<tr>
<td>Amputation secondary to HIT-associated thrombosis</td>
<td>0.54 (0.15–2.03)</td>
<td>0.36</td>
<td>1.22 (0.44–3.39)</td>
<td>0.71</td>
</tr>
<tr>
<td>New thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model A: argatroban</td>
<td>0.29 (0.17–0.50)</td>
<td>&lt; 0.001</td>
<td>0.32 (0.18–0.55)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Model B: argatroban</td>
<td>0.22 (0.11–0.42)</td>
<td>&lt; 0.001</td>
<td>0.27 (0.14–0.55)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age, yr</td>
<td>0.99 (0.97–1.02)</td>
<td>0.47</td>
<td>1.00 (0.98–1.02)</td>
<td>0.69</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.09 (0.54–2.18)</td>
<td>0.82</td>
<td>0.87 (0.48–1.57)</td>
<td>0.64</td>
</tr>
<tr>
<td>White race</td>
<td>0.32 (0.15–0.65)</td>
<td>0.002</td>
<td>0.43 (0.21–0.88)</td>
<td>0.02</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>0.99 (0.97–1.01)</td>
<td>0.22</td>
<td>1.00 (0.98–1.01)</td>
<td>0.75</td>
</tr>
<tr>
<td>Platelet count, × 10^9/L</td>
<td>0.99 (0.98–1.00)</td>
<td>0.048</td>
<td>1.00 (0.99–1.00)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*Model A = regression model with treatment effect only. Model B = regression model with treatment effect, adjusting for patient age, gender, race, weight, and baseline platelet count.
†Compared with nonwhites.
‡Model B including baseline covariates did not converge owing to all patients within one or more categories being censored and hence is not reported.

Table 4—Patients Event Free of the Thrombotic Composite or Its Individual Components by Time-to-Event Analysis*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>HIT</th>
<th></th>
<th>HIT With Thrombosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aragrotoban (n = 321)</td>
<td>Control (n = 139)</td>
<td>p Value, Log Rank</td>
<td>Aragrotoban (n = 376)</td>
</tr>
<tr>
<td>Thrombotic composite</td>
<td>91 (2)</td>
<td>73 (4)</td>
<td>&lt; 0.001</td>
<td>72 (2)</td>
</tr>
<tr>
<td>Death due to thrombosis</td>
<td>99.7 (0.4)</td>
<td>95 (2)</td>
<td>0.0013</td>
<td>98 (1)</td>
</tr>
<tr>
<td>Amputation secondary to HIT-associated thrombosis</td>
<td>98 (1)</td>
<td>97 (2)</td>
<td>0.39</td>
<td>87 (2)</td>
</tr>
<tr>
<td>New thrombosis</td>
<td>93 (2)</td>
<td>76 (4)</td>
<td>&lt; 0.001</td>
<td>83 (2)</td>
</tr>
</tbody>
</table>

*Data are presented as % (SE).
also decreased 2% for each 1-kg increase in body weight in HIT patients without thrombosis (adjusted hazard ratio, 0.98; 95% CI, 0.96 to 0.998, \(p = 0.029\)).

**New Thrombosis:** Regression modeling using these same covariates further demonstrated a significantly reduced relative risk of new thrombosis in white patients, irrespective of the initial HIT presentation (HIT: adjusted hazard ratio, 0.32; 95% CI, 0.15 to 0.65, \(p = 0.002\); HIT with thrombosis: adjusted hazard ratio, 0.43; 95% CI, 0.21 to 0.88, \(p = 0.02\)). In HIT patients without thrombosis, the relative risk of new thrombosis decreased 1% for each \(1 \times 10^9/L\) increase in the baseline platelet count (adjusted hazard ratio, 0.99, 95% CI, 0.98 to 1.00, \(p = 0.048\)). By time-to-event analysis, patients already with HIT-associated thrombosis at diagnosis were significantly more likely to have additional thrombosis in both the treatment group (\(p < 0.001\)) and control group (\(p = 0.014\)).

**Death:** The risk of death due to thrombosis was not significantly affected by patient demographic variables or baseline platelet count.
Amputation: For amputation secondary to HIT-associated thrombosis, the Cox proportional hazard model using these covariates did not converge owing to all patients within one or more categories being censored. Thus, results of the analysis were unable to be generated.

Bleeding: Major bleeding rates were not different between the argatroban-treated patients (6%) and control patients (7%, \( p = 0.74 \)).

Limitations

This study is retrospective in design. However, all study data, including outcomes and patient characteristics, were from prospective, multicenter clinical studies of argatroban therapy in HIT. The similarity across the studies5,6 in their design and the consistency in their conclusions supported a retrospective, combined analysis, allowing evaluation of the antithrombotic effects of argatroban and possible risk factors for HIT-associated thrombotic events in a relatively larger population of HIT patients.

The analysis of the antithrombotic effects of argatroban therapy uses a historical control group as comparator. The prospective studies of direct thrombin inhibition with argatroban5,6 or lepirudin7,8 in HIT were conducted before approved therapies were available and placebo control was unethical; hence, comparisons were made with historical control patients. In the argatroban studies, approaches to minimize possible sources of bias in the control group have been described and included the use of prospectively defined, objective means for identifying potential control subjects, application of the same eligibility criteria as used for the prospectively treated patients, and two-tier medical review with adjudication of potential control subjects.5,6 Potential biases, if operational, were believed to be more likely to mask, rather than exaggerate, true between-group differences. Although the treatment and control groups had some baseline differences in their race and gender distributions, the groups were generally well matched, and hazard risk analyses demonstrated significant antithrombotic effects of argatroban, even when adjusting for baseline covariates.

Discussion

HIT is a serious complication of heparin therapy that often leads to limb- and life-threatening thrombotic events, including deep venous thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, and limb artery occlusion. In the absence of alternative anticoagulation, despite discontinuation of heparins, thrombosis develops in 38 to 76% of patients with HIT in the days to weeks following HIT onset, often after the thrombocytopenia has resolved.4 HIT should be considered in every patient with thrombosis and a recent (or current) history of heparin therapy or hospitalization, regardless of other causes of thrombocytopenia.14,19 Whenever HIT with or without thrombosis is strongly suspected, heparins should be stopped and alternative anticoagulation should be started as soon as possible.9 Low-molecular-weight heparins can propagate HIT and are contraindicated in this setting. Warfarin should not be used as sole therapy in HIT because it can worsen thrombosis and cause venous limb gangrene; its initiation for chronic anticoagulation should be delayed until adequate parenteral anticoagulation is provided and the platelet count has recovered substantially.6 Argatroban and lepirudin are direct thrombin inhibitors approved for use in the United States in patients with HIT; argatroban is also approved for use in patients with or at risk for HIT undergoing percutaneous coronary intervention.20

Argatroban Antithrombotic Effects in HIT

Prospective studies supporting direct thrombin inhibition therapy in HIT5–8 used as primary end point a composite of death, amputation, or new thrombosis, that is, an end point impacted by both thrombotic- and nonthrombotic-related clinical factors. In this retrospective analysis of 882 patients from the prospective studies of argatroban in HIT, we aimed to characterize more specifically the effects of thrombin inhibition on thrombotic-related events. In contrast with previous studies, therefore, our prospectively defined primary end point was a composite of thrombotic outcomes only, including death due to thrombosis, amputation secondary to HIT-associated thrombosis, or new thrombosis.

We found that argatroban therapy, compared with historical control, exerted consistent and significant antithrombotic benefits in the prospective Argatroban-9115 and Argatroban-915 studies, and the extension Argatroban-915X study,6 without increasing major bleeding. The across-study consistency in findings was striking and supported subsequent robust, combined data analyses. Argatroban, vs control, therapy reduced the risk of the composite of thrombosis-associated outcomes approximately threefold in HIT patients presenting with isolated thrombocytopenia and approximately 2.5-fold in HIT patients presenting with thrombosis. These risk reductions, which compare favorably with the previously reported 1.5-fold to 1.7-fold risk reductions of the composite of outcomes from any causes,5,6 better
reflect the specific antithrombotic actions of argatroban in this setting. Argatroban also significantly reduced the risk of new thrombosis by approximately threefold to fourfold and of death due to thrombosis by approximately fivefold to 12-fold.

There was no significant effect of argatroban on amputation secondary to HIT-associated thrombosis. A retrospective analysis of the amputation events in the prospective studies of argatroban in HIT found that severe ischemia or gangrene was present in 98% of the amputated limbs before argatroban was started, and that amputation was already planned in most patients. Hence, a reduction in amputation rate could not have been expected.

The time-to-event curves between the argatroban and control groups for the thrombotic composite end point and new thrombosis each separated early, almost immediately for HIT patients with thrombosis. This early antithrombotic benefit of argatroban underscores the importance of initiating appropriate therapy immediately on HIT suspicion, especially in HIT patients presenting with thrombosis. The initiation of direct thrombin inhibition therapy should not be delayed pending laboratory confirmation of HIT, which may take hours to days.

**Risk Factors for Thrombotic Outcomes in HIT**

We also investigated the effects of demographic variables and baseline platelet count on the occurrence of HIT-associated thrombotic events. Our findings indicate that: nonwhites are approximately two to three times more likely than whites to progress to a HIT-associated thrombotic outcome, particularly to new thrombosis; women presenting with HIT and thrombosis are 1.7-times more likely than men to have a new HIT-associated thrombotic event; decreased body weight increases the risk of a HIT-associated thrombotic outcome; and a decreased platelet count increases the risk of a new thrombosis (specifically, each 1 × 10^9/L decrease translates to a 1% increase in thrombotic risk).

Female patients, who are more likely than male patients to acquire HIT in the first place, have been shown also to be at increased risk of ischemic stroke in HIT. The severity of thrombocytopenia at baseline has been previously reported to be a significant predictor of untoward outcomes in HIT, which is consistent with our current findings as well as the central role of platelets in HIT pathophysiology. We have newly identified nonwhite patients and lower-body-weight patients as higher-risk subgroups. Most of the nonwhites in the analysis population were black; however, a variety of races were represented and additional investigation would be needed to refine their relative risks.

In both the treatment and control groups, HIT patients with thrombosis at presentation were significantly more likely than patients with isolated thrombocytopenia to have new thrombosis. This suggests that the occurrence of one thrombotic event is an important predictor for a future event, again emphasizing the importance of early antithrombotic therapy in this setting, especially in patients with suspected HIT and thrombosis.

**Conclusion**

Argatroban, vs control, provides effective antithrombotic therapy in HIT patients presenting with or without HIT-associated thrombosis, without increasing bleeding. HIT patients who are at particular risk for thrombotic outcomes include women, nonwhites, and individuals with current HIT-associated thrombosis, lower body weight, or more severe thrombocytopenia.

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